
The role of rectal
hyposensitivity in the
development of
functional hindgut
disorders:
clinical significance and
pathophysiology

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Submitted in partial fulfillment of the requirements
of the degree of Doctor of Philosophy

1 STATEMENT OF ORIGINALITY

I, REBECCA ELIZABETH BURGELL, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

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Date: 19 – 01 – 2014

1.1 Details of collaboration:

Chapter 13:

This work was done in collaboration with Dr. Michal Szczesniak, Department of Gastroenterology, St George Hospital / University of New South Wales, who developed the macros (MATLAB signal processing toolbox, The Math Works, Natick, MA, USA) used in the production of the viscerosensory maps.

Chapter 14

This work was done in collaboration with Dr. Dina Lelic, Dr. Soren Olesen and Prof. Asbjorn Drewes, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark.

Inverse modelling and statistical analysis was performed in conjunction with Dr. Dina Lelic and Dr. Soren Olesen. Dr. Lelic also assisted with data collection. Prof. Asbjorn Drewes supervised the proportion of work undertaken in Denmark, and assisted with data analysis and interpretation of results.

1.2 Peer review Publications

Burgell RE, Lelic D, Carrington E.V, Lunniss PJ, Olesen S.S, Surguy S, Drewes A.M, Scott S.M. Assessment of rectal afferent neuronal function and brain activity in patients with constipation and rectal hyposensitivity. *Neurogastroenterol Motil*. 2013; 25(3):260-7

Burgell RE, Scott SM. Rectal hyposensitivity. *J Neurogastroenterol Motil*. 2012 Oct; 18(4):373-84.

Burgell RE, Bhan C, Lunniss PJ, Scott SM. Fecal incontinence in men: coexistent constipation and impact of rectal hyposensitivity. *Dis Colon Rectum*. 2012 Jan; 55(1):18-25.

Peer reviewed abstracts for presentation at learned societies

Burgell RE, Lelic D, Carrington E.V, Lunniss PJ, Olesen S.S, Surguy S, Drewes A.M, Scott S.M. Assessment of rectal afferent neuronal function and brain activity in patients with constipation and rectal hyposensitivity. *J Gastroenterol Hepatol*. 2012; 27 (supplement 4): 150

Burgell RE, Szczesniak M, Yerragorla P, Carrington EV, Mohammed S, Lunniss PJ, Dinning P, Scott SM. Quality, intensity and location of the urge to defaecate differs between patients with constipation and healthy subjects. *Gastroenterology* 2013; 141 (supplement 1): A1476

Burgell RE, Szczesniak M, Carrington EV, Mohammed S, Lunniss PJ, Scott SM. Quality of perception of the desire to defaecate and viscerosomatic referral patterns differ between patients with chronic constipation and healthy subjects. *Neurogastroenterol motil.* 2012; 24 (supplement 2): A489a

Carrington EV, Burgell RE, Lelic D, Surguy S, Drewes A, Aziz Q, Knowles C, Scott SM. Assessment of rectal afferent neuronal function using evoked potentials in patients with constipation and rectal hyposensitivity – a pilot study. *Br J Surg.* 2011; 98 (supplement 2): 243

Burgell RE, Bhan C, Lunniss PJ, Scott SM. Fecal incontinence in men: Coexistent constipation and impact of rectal hyposensitivity. *Gastroenterology* 2010; 138 (supplement 1): T1345

Burgell RE, Lunniss PJ, Scott SM. Male fecal incontinence the importance of rectal sensory dysfunction. *Neurogastroenterol motil.* 2009; 21 (supplement 1): A65

2 ABSTRACT

Background

Rectal hyposensitivity (RH) is associated with functional hindgut disorders. It is hypothesized to involve afferent pathway dysfunction. However, little is known regarding its clinical impact.

Aims

To assess whether RH is:

- clinically important and associated with specific symptoms;
- secondary to afferent neuronal dysfunction; and
- primarily a pelvic abnormality.

Methods

Epidemiological studies were conducted: (1) a case-controlled study stratified by sensory status, assessing symptoms of constipation and incontinence, health status and quality of life; (2) an observational study exploring RH in faecal incontinence in men; (3) an observational study examining the impact of RH on defaecatory urge.

Pathophysiological studies were also conducted: (1) transmission of visceral sensory information was evaluated using rectal evoked potentials;

(2) somatic sensory function and visceral efferent function were examined in patients with and without RH.

Results

RH is associated with constipation. Patients with RH have more severe symptoms and worse health status and quality of life. Constipated patients report altered defaecatory urge compared to controls, most notably in those with RH.

RH is associated with concurrent constipation and evacuatory dysfunction in males with incontinence.

Patients with RH have delayed evoked potential latencies, without alteration of cortical activation. A proportion have elevated somatic sensory thresholds although efferent function is similar between groups.

Conclusions

1. In patients with constipation, those with RH have a worse clinical phenotype, with poorer health status and quality of life. Patients with constipation, (particularly those with RH), have alteration of defaecatory urge.
2. RH and constipation may contribute to incontinence in males where sphincter dysfunction is less important.

3. RH is associated with delayed afferent transmission indicating primary afferent pathway dysfunction. In a proportion, reflecting a possible generalised sensory neuropathy.

These studies confirm that intact rectal sensation is fundamental to normal hindgut function. Impaired visceral sensation is thus an important therapeutic target.

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FOR LESLEY

7 ABBREVIATIONS USED WITHIN THIS THESIS

ADIS	Anorectal dysfunction impact score
ANOVA	Analysis of variance
ARA	Anorectal angle
BESA	Brain electrical source analysis
BMI	Body mass index
CC	Chronic constipation
CCCS	Cleveland Clinic constipation score
cmH ₂ O	Centimetres of water
CMS	Cortical magnetic stimulation
DDP	Defaecatory desire pressure
DDV	Defaecatory desire volume
EAS	External anal sphincter
EEG	Electroencephalogram
ENS	Enteric nervous system
EMG	Electromyogram
EPs	Evoked potential
FCS	First constant sensation
FCSp	First constant sensation pressure
FI	Faecal incontinence
FS	First sensation
GI	Gastrointestinal

g/mm ²	Grams per millimeter squared
HV	Healthy volunteer
Hz	Hertz
IAS	Internal anal sphincter
IBS	Irritable bowel syndrome
IBS-C	Constipation predominant irritable bowel syndrome
IQR	Interquartile range
Kpa	Kilopascals
LORETA	Laplacian weighted Minimum Norm model
LSMS	Lumbosacral magnetic stimulation
mAmp	Milliamps
MEP	Motor evoked potential
mmHg	Millimetres of mercury
MRI	Magnetic resonance imaging
mSec	Millisecond
MTP	Maximal tolerable pressure
MTS	Maximal tolerable sensation
MTV	Maximal tolerable volume
NS	Normal sensation
OR	Odds Ratio
PDT	Pain detection threshold
RAER	Rectal anal excitatory reflex
RAIR	Rectal anal inhibitory reflex

RED	Rectal evacuatory dysfunction
REP	Rectal evoked potential
RH	Rectal hyposensitivity
RMT	Resting motor threshold
SD	Standard deviation
SMIS	St Mark's incontinence score
SNS	Sacral nerve stimulation
STC	Slow transit constipation
3RH	Rectal hyposensitivity with all three sensory levels elevated
ΔP	Change in pressure
ΔV	Change in volume
μV	Microvolts

8 INTRODUCTION

8.1 Part A: The importance of normal rectal sensation in healthy bowel function

In contrast to the sound understanding of the structural anatomy of the anorectum, the neuronal control of rectal function is poorly established. Thus, a brief overview of rectal anatomy will be provided, prior to a more detailed analysis of contemporaneous knowledge of the physiology, sensory and motor control of the anorectum.

8.1.1 Anorectal anatomy

In simplistic terms, the role of the rectum and anus appears straightforward; to contain a gradually increasing faecal bolus so that when sufficient stool has been accumulated, it can be expelled at a socially convenient time. In reality, however, their roles are significantly more complicated (Lunniss *et al.*, 2009).

The rectum begins proximally at the level of the third sacral vertebra (Salerno *et al.*, 2006). It is continuous with the sigmoid colon, although the precise location of its origin is not clearly defined (and is still debated between anatomists and surgeons). Clinically, the point at which the sigmoid colon no longer has a mesentery or appendices epiploicae, or at which the teniae coli become confluent, are often used to designate the

start of the rectum (Salerno *et al.*, 2006). It is approximately 15 – 20 cm in length and extends distally, finishing at the point at which its muscle layers become continuous with that of the anal sphincters (Sinnatamby and Last, 2011). Contrary to its Latin name (rectus = straight), it instead follows the curve of the sacrum with three slight lateral convexities (Figure 1). Proximally, the upper rectum curves towards the right with the middle segment bending towards the left. The lower rectum then returns back towards the right before joining the anal canal (Sinnatamby and Last, 2011).

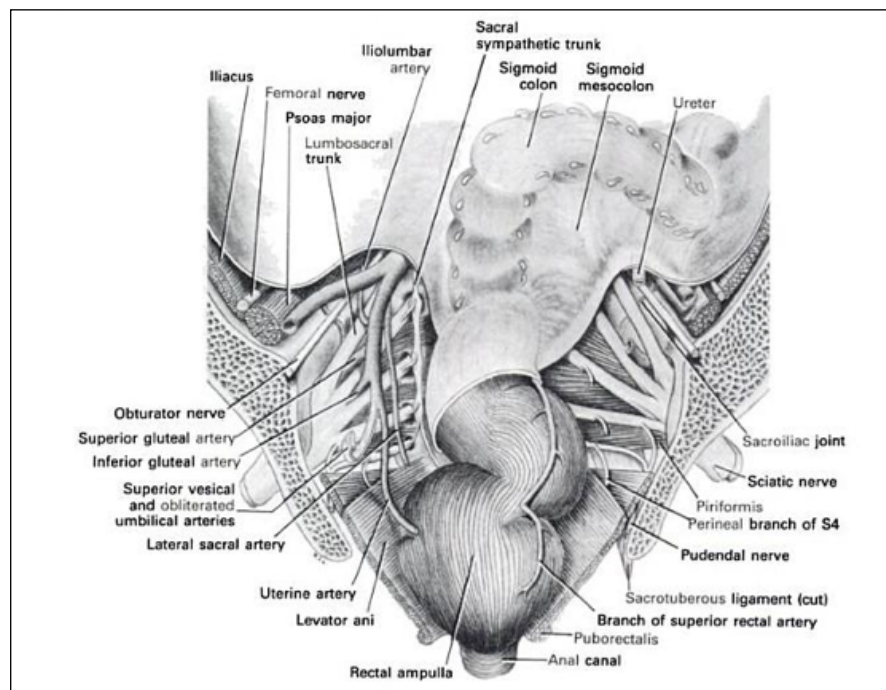


FIGURE 1 – ANATOMY OF THE POSTERIOR SEGMENT OF THE PELVIS - CORONAL SECTION.

WITH PERMISSION (SINNATAMBY AND LAST, 2011)

As the rectum descends towards the anal canal, it traverses the pelvic floor which is formed by the levator ani – pubococcygeus, ileococcygeus, coccygeus and puborectalis muscle (Bharucha, 2006). The distal segment is surrounded by the puborectalis. This muscle has a horseshoe configuration and acts as a sling, lifting the rectum anteriorly to form the anorectal angle (ARA), a possible contributory mechanism for continence, particularly in the setting of sphincter dysfunction (Rao, 2004). It then continues into the anal canal at the level of the perineal body (Sinnatamby and Last, 2011).

In men, the rectum is related anteriorly to the rectovesical pouch (formed by the reflection of the peritoneum forwards over the bladder), the base of the bladder and ureters, the prostate and seminal vesicles, and the ductus deferens (Sinnatamby and Last, 2011). In women, only the rectouterine pouch and vagina lie anteriorly, hence explaining why the development of a rectocele is almost exclusively a female condition (Stoker, 2009). Laterally and posteriolaterally lie the sacral and coccygeal nerves, rectal vessels, the pelvic splanchnic nerves and the sympathetic chain. The rectum is covered by the peritoneum at the front and sides in the upper third of the rectum and in the middle third only anteriorly (Sinnatamby and Last, 2011). The lower third is extra-peritoneal.

In comparison to the colon, the rectum has a complete layer of longitudinal muscle as well as an inner circular muscle layer. The rectal circular fibres

continue distally to become the internal anal sphincter, whereas the longitudinal layers become fibroelastic strands (also known as the longitudinal muscle of the anal canal (Snooks *et al.*, 1986)) in the intersphincteric space (Salerno *et al.*, 2006), with the external sphincter instead formed by coalescence of the lower fibers of the puborectalis muscles. Intraluminally, it is a hollow tube indented by three folds, containing both muscle layer and mucosa, known as the valves of Houston, and is designed to distend and contain the faecal bolus.

Traditionally the rectum is divided into three parts (upper, middle and lower rectum) although embryologically, it develops from only two distinct origins. The upper rectum is derived from the embryological hindgut whereas the lower third arises from the cloaca (Bharucha, 2006). This is important as the dual embryological origin of the anorectum explains its intricate nerve supply (both somatic and autonomic). Co-ordination of rectal neuronal input, as required for normal defaecation, is thus complex.

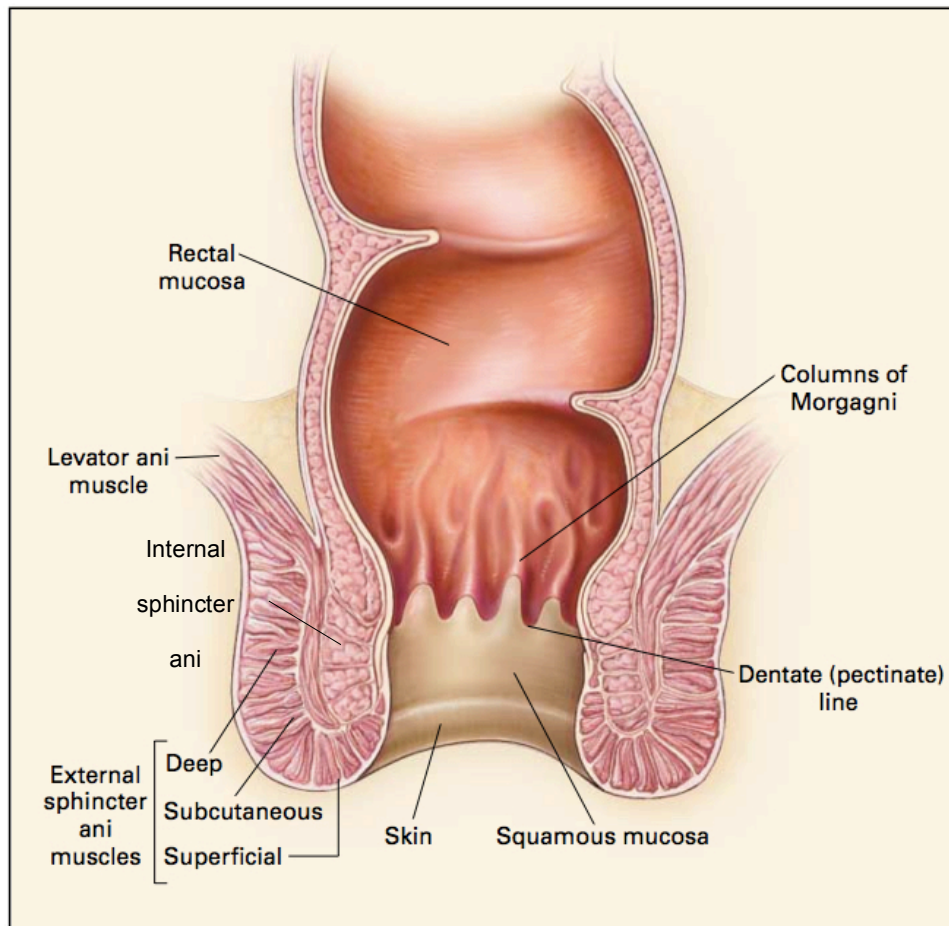


FIGURE 2 – MUSCULATURE OF THE ANORECTUM.

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The most distal point of the gastrointestinal tract is the anal canal. It is considered by anatomists to start 1 -2 cm above the dentate line (Salerno *et al.*, 2006) and is 4 – 6 cm in length (Stoker, 2009), ending at the anal verge. It is enclosed by two muscle rings (the anal sphincters), which serve to preserve continence (Figure 2). Between the sphincters lies the anal longitudinal muscle formed by the continuation of the outer (longitudinal) muscle layer of the rectum. The internal sphincter, as described above, is the continuation of the circular muscle layer of the

rectum. It ends approximately 1 cm proximal to that of the anal canal, so that the most distal portion of the canal contains only external anal sphincter fibers (Stoker, 2009). The external anal sphincter is formed by the lower fibres of the puborectalis sling which, as the canal descends, becomes continuous anteriorly to form a ring (Morren *et al.*, 2001a), (figure 2). The length of the external sphincter is longer laterally (~3 cm) than anteriorly (~1 cm) (Morren *et al.*, 2001a). Traditionally it has been described anatomically as three sections, however this has been difficult to confirm in *in-vivo* imaging studies (Morren *et al.*, 2001a, Stoker, 2009). Posteriorly, the external sphincter contributes fibers to the anococcygeal ligament, and anteriorly to the perineal body and the superficial transverse perineal muscle (Stoker, 2009). Traditionally, the internal sphincter is thought to contribute to the anal resting pressure with the external sphincter responsible for the voluntary squeeze response; clinically, however, this appears to be more complex. The intersphincteric anal longitudinal muscle is important as it results in shorting and widening of the anal canal, leading to eversion of the anal orifice with defaecation (Snooks *et al.*, 1986). The upper 1 cm of the anal canal is lined with columnar epithelium similar to that of the rectum, and the next centimeter with stratified columnar epithelium before a transition to non-hairy and then hairy skin (Bharucha, 2006). In the upper canal lie the anal columns, which are terminals of the superior rectal vessels. The lower edge of the anal columns correlate with the dentate line at which point the epithelium transitions from columnar to skin (Bharucha, 2006). The anal canal ends

at the anal orifice where it opens to the perineum (Sinnatamby and Last, 2011).

Maintenance of continence and the co-ordinated control of the anorectum needed for normal defaecation thus requires a complex interplay of inhibition and activation of both striated and smooth muscle cells (both circular and longitudinal layers) (Lunniss *et al.*, 2009). This is mediated by interactions between the sensory, autonomic and somatic nervous systems (Palit *et al.*, 2012a). Dysfunction either anatomically or neurologically can therefore have marked effects on bowel function.

8.1.2 Anorectal innervation

The regulatory control of the gastrointestinal system is determined through the interaction of the extrinsic nervous system (spinal cord, brainstem, cerebral cortex) and the intrinsic nervous system (enteric nervous system). Furthermore, normal defaecation requires the co-ordination of this visceral system with the somatic nervous system making the innervation of the anorectum particularly complex.

The intrinsic nervous system consists of primary afferent neurons, interneurons and motor neurons (divided into muscle motor neurons, secretomotor neurons and those acting upon entero-endocrine cells) found in a rough ratio of 2:1:1, with each interacting via complex reflex circuits to control effector output (Hansen, 2003). Visceral afferent

information is also transmitted to the higher centers via extrinsic afferent neurones (Figure 3) which project alongside the autonomic efferent fibres to the spinal cord before eventually reaching the cortex (Berthoud *et al.*, 2004). Motor components of the enteric nervous system receive local signals from sensory enteric neurons as well as descending control from the efferent parasympathetic and sympathetic autonomic nervous system (Figure 3). The interplay between each component of the sensory pathways is critical to the sensory output produced. This is because stimuli are processed differently depending on the overall excitability of the system. However, for ease of understanding, each system will be initially considered separately before their interactions are more closely examined later.

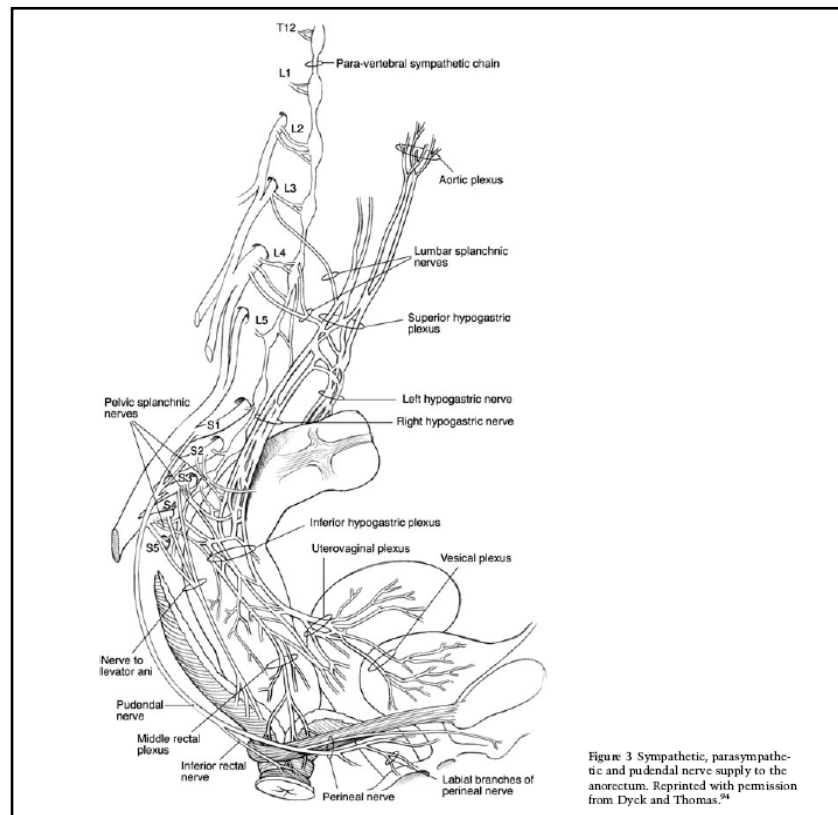


FIGURE 3 – SYMPATHETIC, PARASYMPATHETIC AND SOMATIC (PUDENDAL) NERVE SUPPLY TO THE ANOECTUM

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8.1.2.1 Sensory components of the anorectum

8.1.2.1.1 Sensory components of the enteric nervous system

To date the majority of our understanding of the function of the enteric nervous system comes from animal studies, predominantly in the guinea pig ileum and, to a lesser extent, larger animals (i.e. pigs). In general, the sensory component of the enteric nervous system consists of primary enteric afferent nerves, which make up approximately 30% of the cell bodies found in the neural ganglia in the bowel wall (Costa *et al.*, 2000, Furness, 2012). Neurons can be classified by chemical coding

(combination of neurotransmitters), location in the intestine, electrical behavior function and, of course, species, which can lead to significant confusion (Costa *et al.*, 2000, Hansen, 2003). For example, in the guinea pig, “after hyperpolarisation” (AH) neurons, defined by a phasic spike discharge, calcium regulated action potential, slow after hyperpolarisation and multiple long processes, are the predominant sensory neuron with synaptic-type (S-type) neurons, which have sodium driven action potentials, are highly excitable and receive fast excitatory post-synaptic potentials, usually associated with interneurons or motor neurons (Bornstein *et al.*, 2004, Blackshaw *et al.*, 2007). In the human however, AH neurons are exceedingly rare with instead the majority being S-type (Schemann and Neunlist, 2004). Studies performed in animals thus need to be interpreted with caution.

Sensory afferents of the enteric nervous system have cell bodies within the gut wall. They are located in the main two neural plexi, the myenteric plexus and submucosal plexus (figure 3).

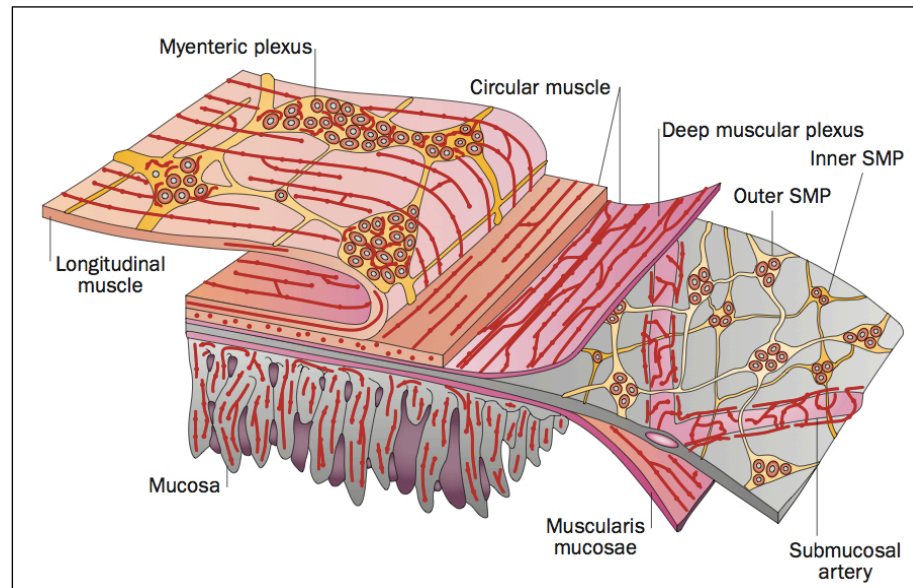


FIGURE 4 – THE ORGANISATION OF THE ENTERIC NERVOUS SYSTEM (ENS) IN HUMANS.

THE ENS HAS TWO GANGLIONATED PLEXUS, THE MYENTERIC PLEXUS (BETWEEN THE CIRCULAR AND LONGITUDINAL MUSCLE LAYERS) AND THE SUBMUCOSAL PLEXUS (SMP) THAT LIES IN THE GUT WALL SUBMUCOSA. REPRINTED BY PERMISSION FROM MACMILLAN PUBLISHERS LTD: NAT REV GASTROENTEROL HEPATOL. (FURNESS, 2012) COPYRIGHT (2012)

Primary afferent neurons (also known as intrinsic primary afferent neurons or IPANs) are mechanoreceptive, chemoreceptive and thermoreceptive (Hansen, 2003). The mechanoreceptors are divided into subgroups: the first group consists of wide-range mechanoreceptors, which are activated at low intensity to indicate non-painful and generally subconscious sensation such as benign distension. Activation of these neurons results in contraction and peristalsis of the musculature (Hansen, 2003). This group is predominantly located in the myenteric ganglia (Berthoud *et al.*, 2004). The second subgroup consists of high threshold mechanoreceptors, located along blood vessels in the submucosa and mesenteric ganglia

(Berthoud *et al.*, 2004). These receptors are triggered only in the setting of painful stimuli and otherwise have low resting activity (Knowles and Aziz, 2009). A third group of receptors has also been proposed called “silent nociceptors” which are only “switched on” or sensitised after exposure to inflammation (Knowles and Aziz, 2009). Sensory neurons contain a number of neurotransmitters (i.e. Substance P, VIP) which when other surrounding neurons are exposed, as in the setting of ischaemia or infection, results in increased sensitivity (Hansen, 2003). It is hypothesised that these receptors may be involved in the development of hypersensitivity and chronic pain (Cervero and Laird, 1999). Primary afferent mechanoreceptors respond to distension and are thought to sense stimuli through a number of mechanisms. Firstly, submucosal afferent neurons (myenteric afferents only respond in the presence of secondary input) can respond directly to distortion via mechanosensitive ion channels or, secondarily, in response to the release of local neurotransmitters such as 5-HT from deformed neuroendocrine cells (Raybould *et al.*, 2004, Blackshaw *et al.*, 2007).

Primary afferent neurons also sense chemical changes in the lumen (i.e. secondary to pathogens, parasites, etc.). As sensory neurons themselves do not physically cross the epithelium (Raybould *et al.*, 2004) and therefore are not exposed directly to the intestinal lumen, their ability to “sense” such chemical changes are mediated in a paracrine manner via “intestinal taste buds” such as enterochromaffin cells which release

neurotransmitters in response to luminal conditions (Blackshaw *et al.*, 2007) such as toxin release from bacterial infection.

To effect end organ changes, be it alterations in motility, blood flow or luminal secretion, primary afferent neurons communicate directly with interneurons and motor neurons (including muscle neurons, secretomotor neurons and endo-endocrine cells). They also communicate with specialized viscerofugal neurons, essentially a sensory interneuron with its cell body in the gut wall but which projects externally to the prevertebral ganglia. These connections create a neural circuit with descending sympathetic neurons (Hibberd *et al.*, 2012), creating a secondary inhibitory reflex arc to the motor and secretomotor pathways (Furness, 2003, Furness, 2006). In the rectum, these project to the inferior mesenteric ganglion (Brookes, 2001) and respond to distension of the gut (Furness, 2003). These reflex arcs are responsible for creating the propagating movements that transfer luminal contents, both in anterograde and retrograde directions, over large segments of the gut.

8.1.2.1.2 Sensory components of the extrinsic nervous system

Whereas the upper gastrointestinal tract and small intestine can function independently of the central nervous system (CNS), the colon and rectum are more highly regulated by descending influences (Furness, 2012).

The afferent component of the so called “brain-gut axis” involves spinal afferent nerves which follow the path of the somatic and efferent autonomic nerves (Brock *et al.*, 2009) to the spine, albeit with information transmitted in the opposite direction. They have cell bodies in the dorsal root ganglia (Figure 5) and synapse with second order neurons in the spinal cord. Like viscerofugal neurons, these ascending spinal afferents also give off branches to the local sympathetic ganglia creating both spinal and ganglionic reflex circuits (Grundy *et al.*, 2006). Visceral afferent neurons account for approximately 10% of the afferent nerves in the spinal cord (Grundy *et al.*, 2006). These second order spinal neurons also receive somatic and visceral stimuli, accounting for the commonly observed symptom of referred pain (Berthoud *et al.*, 2004). Ultimately, the sensory pathway projects to the thalamus where it is then relayed to the higher centres (Berthoud *et al.*, 2004, Brock *et al.*, 2009) (Figure 5).

Spinal afferents are divided into two groups: the splanchnic nerves, which predominantly supply the colon, and the pelvic afferents which supply the rectum (Sharma *et al.*, 2009). Approximately a third of pelvic nerves are thought to be afferent in nature (Knowles and Aziz, 2009). Radiotracer studies (Brookes, 2001, Berthoud *et al.*, 2004) have identified that spinal afferents have peripheral endings, which terminate in the serosa and mesenteric attachments where they are associated with blood vessels and the muscle layers. In the muscle layers they end either as axonal varicosities or as intraganglionic laminar endings (IGLE's) (Grundy *et al.*, 2006). IGLE's detect sheer forces and are found only in the rectum and

upper gut and not in the colon (Berthoud *et al.*, 2004). Extrinsic afferent neurons also communicate directly with the enteric ganglia in the myenteric plexus and as well as terminating in the mucosa of the bowel wall where they are often associated with submucosal arteries (Knowles and Aziz, 2009).

Similar to the enteric afferents, extrinsic sensory neurons “sense” by direct deformation of ion channels or by response to the release of neurotransmitters by nearby cells. They are both mechano- and chemoreceptive. Nerve terminals in the mesentery and serosa respond to deformation of the mesenteric attachments, whereas nerves terminating in the muscle respond to distension and contraction (Berthoud 2006). Extrinsic sensory neurons are also modulated by the release of inflammatory mediators resulting in peripheral sensitization.

8.1.2.1.3 Sensory components of the somatic nervous system

The somatic nervous supply is responsible for sensation from the anal skin. It is supplied by the pudendal nerve, which arises from the anterior primary rami of S2, 3 and 4 and is delivered to the anal canal via the inferior rectal branch (Chan *et al.*, 2005b, Bharucha, 2006). While the pudendal nerve supplies anal sensation, rectal sensation above the lower third is not influenced by pudendal nerve block indicating other pathways predominate (Chan *et al.*, 2005b).

8.1.2.2 Motor components of the anorectum

8.1.2.2.1 Motor components of the enteric nervous system

The motor control of the bowel is provided by a number of different motor effector neurons. These are divided into inhibitory and excitatory groups (Bornstein *et al.*, 2004), which act upon the circular or the longitudinal muscles. The majority of understanding in this field again comes from the guinea-pig where the motor neurons have been found to make up 12% (inhibitory) and 10% (excitatory) of the myenteric neurons (Bornstein *et al.*, 2004). Motor neurons have their cell bodies in the mucosal plexus and muscularis plexus, and project in an oral (excitatory neurons) or aboral (inhibitory neurons) direction to smooth muscle bundles (Bornstein *et al.*, 2004). The co-ordinated activation of these neurons contribute to the contraction / relaxation patterns, which generally propel contents in an anal direction (Brookes *et al.*, 2009). There is no directional preference in those neurons that innervate the longitudinal muscle (Bornstein *et al.*, 2004).

8.1.2.2.2 Motor components of the extrinsic nervous system

The rectum receives its efferent supply via sympathetic and parasympathetic fibers of the autonomic nervous system and, in the lower third, the somatic nervous system (Knowles *et al.*, 2001). The parasympathetic supply originates from the ventral rami of the 2nd, 3rd and 4th sacral nerves and forms the inferior hypogastric plexus which supplies the rectum via the rectal plexus. The sympathetic fibres, in contrast, arise

from the paravertebral sympathetic chain. These fibres form the superior hypogastric plexus with descending fibres from the aortic plexus before meeting the parasympathetic fibres in the inferior hypogastric plexus (Bharucha, 2006). These neurons synapse with the enteric nervous system in the muscularis and submucosa to modulate the motor reflexes of the bowel. Studies in diarrhoea-predominant irritable bowel syndrome (IBS) have found a tendency for the sympathetic system to be more active and the parasympathetic components to be suppressed (Karling *et al.*, 1998, Adeyemi *et al.*, 1999, van Orshoven *et al.*, 2006). Studies in constipation-predominant IBS, by contrast, have shown a significant association with parasympathetic dysfunction (Aggarwal *et al.*, 1994). Similarly, sympathetic nervous system dysfunction is associated with numerous functional pain syndromes whereas stimulation of the parasympathetic system has been shown to decrease pain (Kirchner *et al.*, 2006).

8.1.2.2.3 Motor components of the somatic nervous system

The rectum also receives innervation from the somatic nervous system via the pudendal nerves. This dual innervation has been shown to be restricted to the lower third of the rectum (<7 cm from anal verge).

8.1.3 The role of sensation in normal defaecation

8.1.3.1 Interplay of the enteric, extrinsic and somatic nervous system

The propulsion of luminal contents from colon to rectum, as well as the initiation and completion of evacuation, depends on multiple organised processes created by the interaction between sensory and motor pathways in the gut, sympathetic ganglia, spine and higher cortical centres.

As the colon fills, mechanoreceptors and chemoreceptors of the intrinsic and extrinsic afferent pathways are stimulated. This initiates a series of pre-determined propagating motor patterns arising from enteric and sympathetic ganglionic reflex arcs, resulting in movement of luminal contents. This ultimately leads to filling of the rectum, which is able to distend to accommodate increasing amounts of stool. This process is both passive (related to bowel wall structure) and active (mediated via controlled smooth muscle relaxation) (Rao *et al.*, 2002). When a sufficient volume of stool distends the rectum, the perception of rectal fullness is communicated to the cortex by the extrinsic afferent pathways. This process is reduced after low spinal anaesthesia or transaction of the spinal cord above S2 (Nathan and Smith, 1953) indicating that intact sacral pathways are critical. As the volume of stool increases, a graded response from initial awareness to urge to defaecate is experienced. Onset of defaecatory urge is associated with a transient contraction of the puborectalis muscle termed the sensorimotor response (Cheeney *et al.*,

2011), which is thought to prevent the accidental expulsion of rectal contents before the initiation of voluntary evacuation (De Ocampo *et al.*, 2007). Defaecatory urge appears to be predominantly mediated via pressure distortion of the rectal wall as early studies have indicated that the urge to defaecate appears to be independent from volume or weight (Broens *et al.*, 1994). Rectal distension also results in relaxation of the internal anal sphincter (enteric inhibitory motor neurons) and contraction of the external anal sphincter (enteric excitatory motor neurons) as a result of the recto-anal inhibitory reflex. In healthy individuals, transient relaxation of the internal anal sphincter occurs every 8 – 10 minutes (Bajwa and Emmanuel, 2009). This allows sampling of the rectal contents (Bajwa and Emmanuel, 2009) by the more sensitive anal mucosa and has been hypothesised to allow discrimination between solid, liquid and gas. The reflex is dependent on an intact enteric nervous system and is absent in patients with Hirschprung's disease, a congenital absence of enteric ganglia, although it is modulated by descending influences (Scott and Gladman, 2008). The RAIR requires intact rectal sensation and an appropriate degree of rectal stimulation (Bajwa and Emmanuel, 2009), although sphincter relaxation may occur in the absence of sensory awareness. For instance, while increased rectal distension volumes are required to induce the reflex in patients with rectal hyposensitivity, the RAIR response may still occur below sensory threshold (Remes-Troche *et al.*, 2010) suggesting cortical awareness is not essential. However whether alteration in rectal sensory function results in an altered number

of sampling episodes in patients with incontinence or constipation overall is unknown. Although in the presence of intact rectal sensation, the degree of sphincter relaxation depends on the level of rectal distension (Sun *et al.*, 1990c) indicating that normal rectal sensation is important. In patients with abnormalities of the RAIR (i.e. spinal cord injury), incontinence correlates with increased duration of sphincter relaxation and recovery, whereas constipation correlates with diminished relaxation (Thiruppathy *et al.*, 2012) following rectal distension. The sampling reflex or RAIR is thought to contribute to the maintenance of continence by recognising and accurately distinguishing rectal contents, allowing evacuation at a socially acceptable time.

When defaecation is deemed appropriate, toileting posture is assumed and defaecation initiated. This process requires elevation of rectal pressures generated by straining and activation of the abdominal muscles (Denny-Brown and Robertson, 2004) along with simultaneous relaxation of the anal sphincters to create a pressure gradient from rectum to anus. Rectal contractions may also occur during defaecation, but these do not appear to be essential to evacuation (Mertz, 2003). Relaxation of the anal canal following initiation of defaecation is mediated via spinal reflex arcs (Furness, 2012), as once initiated, reflex rectal emptying is generally completed even in the setting of spinal cord injury. While voluntary control is lost in such patients, experimental models have shown that defaecation can be initiated and completed by stimulation of the “lumbosacral

defaecation area” which appears to be sensitive to centrally acting ghrelin agonists (Whitehead *et al.*, 1999, Furness, 2012). If defaecation is not socially appropriate or if the urge to defaecate is ignored, ongoing rectal distension results in inhibition of colonic motor activity via viscerovisceral inhibitory reflexes (Law *et al.*, 2002).

In summary, intact sensory pathways, both rectal and anal, are essential to normal defaecation (Bajwa and Emmanuel, 2009). Accordingly, disruption of normal anorectal sensory function has the potential to contribute to significant defaecatory dysfunction. Subsequent sections will expand upon the clinical syndromes associated with disruption of healthy enteric and extrinsic neuronal pathways with a particular focus on sensory dysfunction.

8.2 Part B: Functional hindgut disorders

8.2.1 Constipation

8.2.1.1 Definition of constipation

One of the greatest challenges of research into symptoms of constipation is addressing the heterogeneity of the disorder as a whole, as well as the vagaries of its definition. There is great controversy as to whether constipation is best defined symptomatically or physiologically, a conflict which remains to be resolved. Historically, constipation has been confirmed when the patient reported hard stools, infrequent defaecation or evacuatory dysfunction (Lembo and Camilleri, 2003). However, patients who fulfill these criteria often report perfect satisfaction with bowel function, whereas other patients with only minor symptoms describe significant morbidity.

The current nomenclature is also confusing. “Obstructed defaecation,” “rectal evacuatory dysfunction (RED),” “dyssynergic defaecation,” “anismus,” “functional obstruction,” “normal transit constipation,” “slow transit constipation” or “colonic inertia” among others, have all been used to describe constipation. In an attempt to overcome these difficulties, the ROME III criteria (Longstreth *et al.*, 2006) was established to guide diagnosis, treatment and research. This system is not without criticism, particularly in regards to the distinction between irritable bowel syndrome (IBS) with constipation and functional constipation (Chogle *et al.*, 2010,

Wong *et al.*, 2010) and its inability to consider a number of common symptoms described by constipated patients such as bloating or pain with defaecation.

As a result, the definition of constipation used in this thesis is that provided by the American College of Gastroenterology Chronic Constipation Task Force Members. This defines constipation as “unsatisfactory defaecation characterised by infrequent stools, difficult stool passage or both” (American College of Gastroenterology Chronic Constipation Task Force, 2005a). By adopting this definition, patients will not be excluded on the grounds that they have abdominal pain. Therefore patients with both functional constipation and IBS with constipation will be included within the study group. In addition, to ensure patients meet the criteria for chronicity, symptoms should be present for a minimum of three months.

8.2.1.2 General causes of constipation

Constipation is often a symptom of an underlying pathology or disease, and primarily these should be investigated for and excluded. The list of possible diagnoses resulting in secondary constipation is vast (Table 1).

TABLE 1 – SECONDARY CAUSES OF CONSTIPATION

(CHATOOR AND EMMANUEL, 2009)

Structural	Neurological	Myopathic	Other
Tumour Stricture	Spinal cord injury MS Parkinson's disease Aganglionosis	Systemic sclerosis Amyloidosis	Dehydration Immobility Pregnancy Diet

Congenital	Medication	Metabolic	Psychological
Hirschsprug's disease Imperforate anus Anorectal atresia	Opiates Psychiatric medication Cardiac medication Diuretics Parkinson's medicine Anticholinergic Iron	Diabetes Hypokalaemia Hypomagnesia Hypercalcaemia Hypothyroidism Hyperpara-thyroidism	Abuse Eating disorders Affective disorders Chronic pain

8.2.1.3 Chronic constipation

A diagnosis of chronic “primary” or “idiopathic” constipation is given to those who have undergone appropriate investigations and examinations to exclude a structural or organic cause for their symptoms.

8.2.1.3.1 Epidemiology of chronic constipation

The largest population based studies and quality meta-analyses (Talley, 2004, Siproudhis *et al.*, 2006, Peppas *et al.*, 2008, McCrea *et al.*, 2009,

Suares and Ford, 2011) suggest that up to one in seven individuals suffer from symptoms of chronic constipation. Approximately one-third of these seek medical help, resulting in a considerable economic burden. It is estimated that constipation is responsible for 1.7 billion USD a year in health costs in the United States (Everhart and Ruhl, 2009, Cook *et al.*, 2009), with treatment costs estimated at 7,522 USD per patient (Cook *et al.*, 2009). Chronic constipation appears to be three to four times more common in women (Chatoor and Emmanuel, 2009, McCrea *et al.*, 2009) with prevalence increasing with age and infirmity (McCrea *et al.*, 2009).

8.2.1.3.2 Current classification of chronic constipation

Effective management of constipation is dependent on adequate classification of predominant subtype. Unfortunately, symptoms have been shown to be a poor predictor of this (Grotz *et al.*, 1994, Koch *et al.*, 1997, Glia *et al.*, 1998, Mertz *et al.*, 1999b, Rao *et al.*, 2004a). Patients are generally classified as having a disorder of evacuation (rectal evacuatory disorder: RED), disorder of colonic transit (slow transit constipation: STC), or in many, an overlap of both (Cook *et al.*, 2009).

RED may be sub-classified into “functional” obstruction (dyssynergic defaecation) (Figure 7) or mechanical obstruction (e.g. secondary to intussusception or rectocoele). Functional obstruction to defaecation (dyssynergic defaecation) can be detected either during anorectal manometry studies or by functional imaging studies such as defaecating

proctogram. During anorectal manometric studies (see section 10.3.3.1) dyssynergia is diagnosed if there is abnormal anal and rectal pressure profiles during attempted strain. Effective evacuation requires a complex coordinated sequence of events, in that the rectal pressures rises while there is simultaneous relaxation of the puborectalis and anal sphincter. In almost a third of patients with constipation (Nyam *et al.*, 1997), incoordination of this process results in obstruction to defaecation (Rao, 2008). Anorectal manometry is helpful in determining the type of dyssynergia (type I = raised rectal and anal pressure simultaneously, type II = minimal elevation of rectal pressure with raised anal pressures, type III = raised rectal pressures but failure of the anal canal to relax, and type IV = absent increased rectal pressure and poor relaxation of anal canal) by providing simultaneous measurements of rectal and anal pressures during simulated defaecation (Rao *et al.*, 2005).

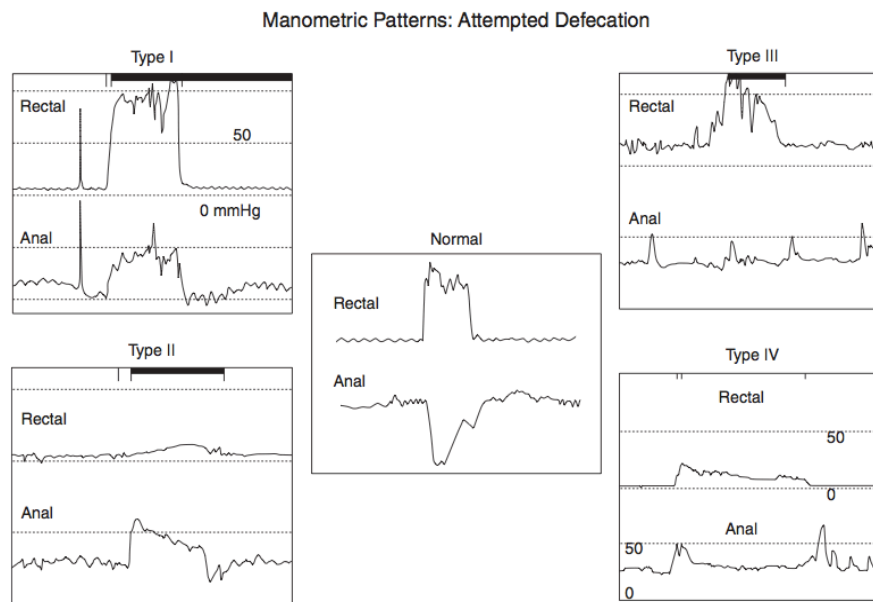


FIGURE 6 – MANOMETRIC PATTERNS OF DYSSYNERGIC DEFAECATION.

NORMAL = RISE IN RECTAL PRESSURE WITH SIMULTANEOUS FALL IN ANAL PRESSURES. TYPE 1 = ADEQUATE PROPULSIVE FORCE BUT INCREASED ANAL PRESSURES WITH STRAIN, TYPE II = POOR PROPULSIVE FORCE WITH INCREASED ANAL PRESSURES WITH STRAIN, TYPE III = GOOD PROPULSIVE FORCE BUT NO ANAL RELAXATION WITH STRAIN, TYPE IV = POOR PROPULSIVE FORCE AND NO ANAL RELAXATION WITH STRAIN. REPRODUCED FROM (RAO AND SINGH, 2010) WITH PERMISSION FROM ELSEVIER.

In contrast, dyssynergia is diagnosed by proctography (see 10.3.3.2) when there is failure of the anal canal to open during defaecation or failure of relaxation of puborectalis (Scott and Gladman, 2008, Lunniss *et al.*, 2009), as evidenced by an inability of the anorectal angle (Agachan *et al.*, 1996b) to open (become obtuse) during defaecation. Dynamic imaging studies such as proctography also provide information as to the presence and clinical significance of structural abnormalities such as rectocele and intussusception, which may also lead to evacuatory obstruction.

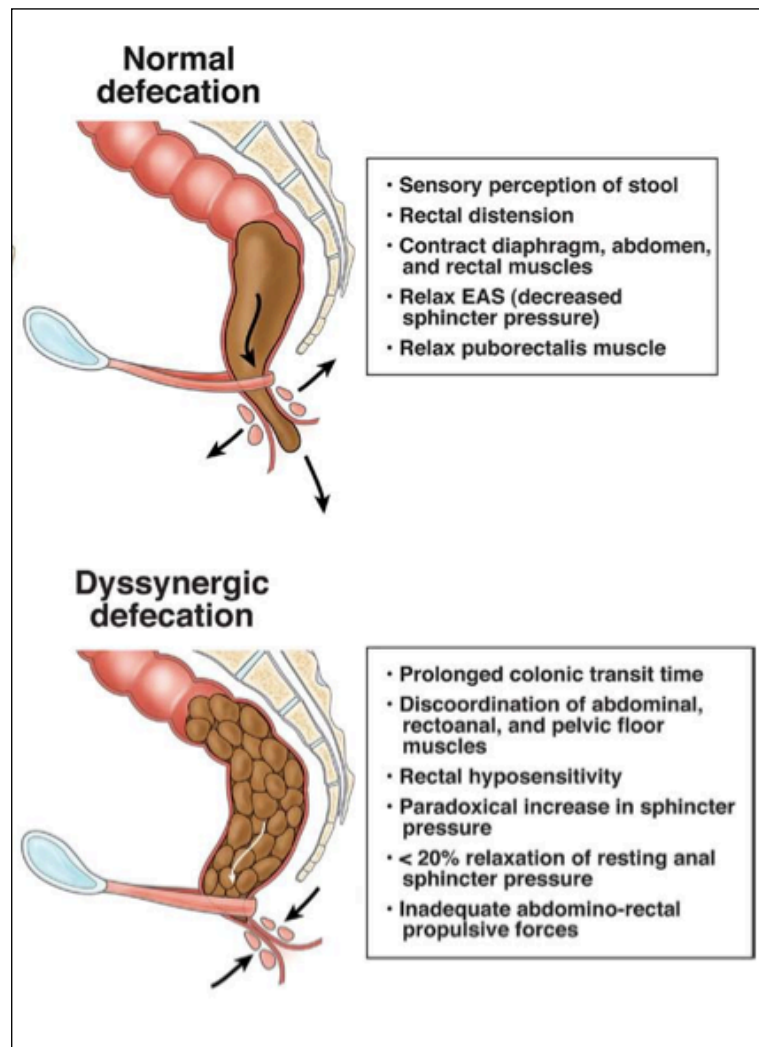


FIGURE 7 – SCHEMATIC DIAGRAM OF NORMAL DEFAECATION (TOP) IN COMPARISON TO DYSSYNERGIC DEFAECATION (BOTTOM).

IN DYSSYNERGIC DEFAECATION, THE PUBORECTALIS MUSCLE (SHOWN AS A SLING AROUND THE LOWER RECTUM) AND ANAL CANAL (ARROWS) FAILS TO RELAX WITH ATTEMPTS AT EVACUATION. REPRODUCED FROM (RAO, 2010) WITH PERMISSION FROM ELSEVIER.

Slow transit constipation is generally diagnosed when individuals have prolonged gut transit time on either radio-opaque marker studies (where the patient consumes an inert radio-opaque marker and then undergoes a plain abdominal X-ray after a defined period of time) or with scintigraphic

techniques using consumed radioisotopes (Rao *et al.*, 2005). Recently a number of advanced techniques have been developed to more accurately measure colonic transit and/or motility such as colonic manometry or wireless motility capsule although these are not in widespread clinical use (Rao *et al.*, 2009, Dinning and Scott, 2011).

Many patients, following comprehensive assessments described above and in more detail in Chapter 10, may also have no pathological abnormality on physiological investigation, termed “normal transit” constipation (Mertz *et al.*, 1999a); although this may be a reflection of the testing tools being “too blunt”. As a result the true proportions of sub-groups within the condition as a whole remain unclear. However, a recent study by Ragg *et al.* (Ragg *et al.*, 2011) in 541 patients suggested that isolated colonic inertia might be more rare than previously thought. It is hoped that advanced investigative techniques used within this thesis may help to overcome these challenges and provide a clearer sub-classification of patients.

8.2.1.4 Current understanding of the pathophysiology of chronic constipation

8.2.1.4.1 Role of motor dysfunction in constipation

8.2.1.4.1.1 Alterations in Colon motility

Chagas disease, which results from an acquired degeneration of colonic neurons induced by an infection by *Trypanosoma Cruzi* protozoan, emphasises the importance of the enteric nervous system in the development of constipation. In this classic example, patients develop severe constipation and progressive colonic dilation leading to megacolon following exposure to the protozoan.

Given our understanding of such enteric neuropathies, the most widely accepted pathophysiological mechanism of chronic constipation is colonic dysmotility. This can be indirectly measured using transit studies (radio-opaque marker studies and scintigraphy) which is frequently prolonged (median 52% of individuals studied (Rao *et al.*, 2005)), although scintigraphic studies have, thus far, been unable to distinguish symptomatically classified subtypes of constipation (Zarate *et al.*, 2008). This is perhaps because such studies are only surrogate markers for colonic motor activity as they are also influenced by stool consistency and / or composition. More sensitive techniques (pan-colonic manometry), which directly records colonic contractile activity, may in the future reveal more specific biomarkers for the conditions and its subtypes, opening up multiple new research and treatment opportunities. Preliminary results are,

to date, encouraging (Dinning *et al.*, 2004, Dinning *et al.*, 2009b, Dinning *et al.*, 2010, Rao and Singh, 2010) clearly showing that colonic motor activity is dysregulated in patients with slow transit constipation.

Increased colonic compliance (increased distensibility of the bowel wall), possibly reflecting a generalised reduction in colonic contractility (Ravi *et al.*, 2010) is also associated with the development of both STC and RED, suggesting both rectal biomechanical properties and also connective tissue changes may play a role in influencing bowel motility independent of the nervous system. This is supported by a study which has shown 40% of patients with normal transit constipation demonstrate alterations in postprandial and fasting colonic tone (Ravi *et al.*, 2010), which may influence motility of the gut. Joint hypermobility (a benign genetic disorder with increased laxity of connective tissue) is also emerging as a potential contributing factor in the development of hindgut dysfunction (Mohammed *et al.*, 2010).

8.2.1.4.1.2 Alterations in rectal motility

The role that the enteric nervous system of the rectum plays in the development of hindgut dysfunction is best highlighted by Hirschprung disease. In this condition, congenital aganglionosis affects a short segment of the distal bowel. As a result, despite intact musculature, as well as an otherwise normal colon, there is lack of propulsive function within the affected segment. Patients with Hirschprung's disease develop

severe constipation usually presenting in the neonatal period due to failure to pass meconium. If the affected segment is not surgically removed, the small area of segmental dysfunction can lead to death via its resultant effects on the proximal bowel.

When measuring rectal motor function directly, patients with chronic constipation have reduced responses to pharmacological (bisocodyl) and physiological (ingestion of meal) stimulations (Lunniss *et al.*, 2009) when compared to healthy individuals. There is also a reduction in the number and amplitude of rectal motor complexes, which may reflect impaired intrinsic rectal neuronal function (Bassotti *et al.*, 1994). These findings are seen in both slow transit constipation (STC) and in rectal evacuatory dysfunction (RED). Consequently, RED has also been thought to be primarily a motor disorder, with the role of afferent dysfunction relatively overlooked. Emerging research suggests, however, that rectal hyposensitivity is commonly associated with RED indicating that it is a disorder of both motor and sensory dysfunction (Gladman *et al.*, 2003a, Burgell *et al.*, 2012).

Ultimately, the result of these abnormalities is failure of propulsion of the colonic contents towards the anus resulting in an overall appearance of either slowed colonic transit, evacuatory dysfunction or both. Nevertheless, whether sensory abnormalities are clearly associated with motor dysfunction has not yet been clearly established.

8.2.1.4.2 Role of sensory dysfunction in constipation

Although the co-existence of sensory dysfunction and constipation was first noted in 1940 by White and colleagues in patients with spinal cord injuries (White *et al.*, 1940), its precise role remains poorly defined. This is due, in part, to difficulties in directly measuring the afferent neuronal function of the bowel as well as the common co-existence of structural or biomechanical abnormalities such as mechanical obstruction, megarectum or hypercompliance of the rectum (Lunniss *et al.*, 2009). The association of sensory dysfunction with hindgut disorders was relatively neglected until the early 1980s when research in the pediatric population found impaired rectal sensation (rectal hyposensitivity: RH) in up to two-thirds of those with chronic childhood constipation (Meunier *et al.*, 1979). Subsequently, RH has been found in one-quarter of adult patients with chronic constipation (Gladman *et al.*, 2003a) where it appears to be more often associated with a functional evacuatory disorder (Gladman *et al.*, 2003b).

Unfortunately, whether sensory abnormalities detected with physiological examination correlate with reported symptoms of constipation innately related to afferent function (such as loss of defaecatory urge) is unknown and requires additional investigation. Loss of defaecatory urge is a commonly reported symptom of constipation and while its pathophysiological importance is unknown, intuitively normal sensory urge must be integral to normal defaecation.

Loss of urge, like rectal hyposensitivity, may be related to a number of physiological abnormalities. Slow colonic transit resulting in poor rectal filling may be a contributor, as may afferent dysfunction, be it receptor mediated, secondary to nerve pathology or mediated via altered cortical processing. Early studies by Harraf *et al* (Harraf *et al.*, 1998) have indicated that in patients with IBS with constipation, loss of defaecatory urge was associated with the need for higher distending pressures to induce sensation of urge to defaecate and discomfort suggesting a correlation between lack of urge and afferent dysfunction. Interestingly, there was no difference noted in constipation symptom profile and, importantly, no difference in colonic transit times were noted. This suggested that lack of rectal filling was not the cause of loss of urge in such patients indicating instead primary afferent dysfunction as the likely mechanism. A study in patients undergoing radical hysterectomy also suggested that afferent nerve damage is behind loss of defaecatory urge. In this study by Barnes *et al.* (Barnes *et al.*, 1991) patients undergoing radical hysterectomy, which is associated with damage to the inferior hypogastric plexus, commonly described loss of defaecatory urge, were found to have elevated sensory thresholds on visceral sensory testing. Unfortunately, neither studies defined normal / abnormal sensory groups so it is unclear what proportion of patients with loss of urge would still have been considered to have normal sensation on current sensory testing protocols. Ultimately, the true clinical impact of sensory dysfunction in patients with hindgut disorders is as yet unknown.

Part B: Functional hindgut disorders cont.

8.2.2 Faecal incontinence

8.2.2.1 Definition of faecal incontinence

Faecal incontinence (FI) is defined as the “involuntary loss of faecal material” (Bartolo and Paterson, 2009), the presence of which has significant negative impact on quality of life (Damon *et al.*, 2006) for the sufferer. FI is a greatly underreported problem (Aitola *et al.*, 2010).

8.2.2.2 General causes of faecal incontinence

Like constipation, faecal incontinence is seen in the setting of multiple organic disorders

TABLE 2 – SECONDARY CAUSES OF FAECAL INCONTINENCE.

(BARTOLO AND PATERSON, 2009)

Inflammatory or infective	Trauma or surgery	Drugs
Crohn's Ulcerative colitis Bacterial GI infections Anal warts HSV	Post obstetric injury Post anal surgery Pouch procedure Injury	α blockers Ca channel blockers GTN Nicotine

TABLE 2. CONT.

Neurogenic	Neoplastic	Congenital	Other
Spina bifida Spinal cord or cauda equina injury MS Parkinson's Diabetes Arachnioditis	Anal cancer Rectal cancer Paget's disease Bowen's disease	Atresia	Radiotherapy Rectal prolapse Irritable bowel syndrome

8.2.2.2.1 Epidemiology of faecal incontinence

Faecal incontinence is reported by approximately 4 – 20%, depending on the definition used, (Johanson *et al.*, 1997, Leung and Rao, 2009, AlAmeel *et al.*, 2010) of the general population, of which less than half are known to the medical system (Ilnyckyj, 2010, Aitola *et al.*, 2010). Traditionally, FI is thought to be more common in women, however more recent community-based studies indicate similar prevalence in males (Whitehead *et al.*, 2009), suggesting the increased frequency seen in earlier studies may be more a reflection of increased health seeking behavior among women, rather than a true sex based difference. FI is seen more frequently in the elderly (2.6% in patients aged 20 - 30 vs. 15.3% in patients older than 70 (Whitehead *et al.*, 2009)) and the infirm (up to 50% of nursing home residents (Leung and Rao, 2009)) and 46% of hospitalised patients (Hughes *et al.*, 2009).

Risk factors that have been identified for faecal incontinence include age, stool consistence and frequency, multiple chronic illnesses and urinary incontinence (Whitehead *et al.*, 2009).

8.2.2.3 Current understanding of the pathogenesis of faecal incontinence

8.2.2.3.1 Role of motor dysfunction in faecal incontinence

Continence relies on the coordinated interaction of the rectum, pelvic floor and the anal sphincters (Bajwa and Emmanuel, 2009). This requires both conscious and unconscious pelvic muscle control. Faecal incontinence occurs when normal continence mechanisms are overwhelmed. This may be secondary to dysfunction of the anal sphincter mechanism (traditionally thought to be the predominant mechanism as a result of obstetric or surgical injury), as a result of alteration in stool consistency (either faecal impaction or diarrhoea), or as an effect of altered rectal or anal sensation (tenesmus, urgency). Alteration in the normal motor function of the colorectum may also contribute to, or underlie, compromise of the continence mechanism.

8.2.2.3.1.1 Alterations in colonic motility

Colonic motility influences continence via its effect on stool consistency and transit speed. If colonic motility is significantly altered, symptoms can result in the setting of intact sphincters. For example, it is not uncommon for patients with severe infective diarrhoea to suffer from incontinence

when normal continence mechanisms are overwhelmed by the presence of profuse liquid stool. Assessment of stool consistency is critical in patients with incontinence and, in the presence of loose stool, treatment with increased fibre, loperamide or codeine may be beneficial, with the aim to suppress colonic motility.

Manometric studies have found that patients with FI have increased low and high amplitude pressure waves in the descending and sigmoid colon compared to healthy individuals (Herbst *et al.*, 1997, Rodger *et al.*, 2010). Neuromodulation therapy (i.e. sacral nerve stimulation [SNS]) has been postulated to mediate its effects by altering the patterns of colonic propagating sequences (Patton *et al.*, 2013). This perhaps explains why SNS appears to work even in the presence of marked structural sphincter abnormalities (Boyle *et al.*, 2009).

8.2.2.3.1.2 Alterations in rectal motility

There are limited studies as to the role of rectal motility in faecal incontinence. Patients with FI particularly associated with rectal hypersensitivity have an increase in frequency of rectal motor complexes, a marker of enteric neuromotor integrity (Chan *et al.*, 2005a), and the use of amitriptyline results in a decreased amplitude of rectal contractions allied to symptomatic improvement (Santoro *et al.*, 2000). However, unlike the colon, neuromodulation therapy does not appear to affect rectal motility in patients with FI (Michelsen *et al.*, 2010).

8.2.2.3.1.3 Alteration in anal motor function

Failure of the sphincters to maintain an adequate pressure (above that of rectum), loss of reflex control (i.e. failure to contract during cough), or failure of the puborectalis sling to draw the anorectal junction adequately forwards can all lead to FI. Patients with FI may also have reflexive relaxation of the anal sphincters prior to the development of any defaecatory urge (Sun *et al.*, 1990b) perhaps related to anorectal sensory dysfunction, and may also have increased transient relaxation of the anal sphincters (Miller *et al.*, 1988, Farouk *et al.*, 1994). Sphincter dysfunction commonly results from structural damage to the muscles (e.g. by obstetric injury or surgical disruption) or secondary to a neuropathic process. Furthermore, patients with FI have increased frequency of pudendal neuropathy (Kiff and Swash, 1984).

8.2.2.3.2 *Role of sensory dysfunction in faecal incontinence*

8.2.2.3.2.1 Anal sensory function

Multiple anal canal receptor types have been discovered that respond to pressure, temperature, distension and nociception (Duthie and Gairns, 1960). There is also a body of literature that associates anal hyposensitivity with functional bowel disorders including FI (Felt-Bersma *et al.*, 1997). However, the formal testing of anal sensation is now less common clinically as there is no targeted therapy aimed at influencing anal sensation and there is no evidence to suggest that anal sensation correlates with symptom severity.

8.2.2.3.2 Rectal sensory function

There is a clear clinical correlation between faecal urgency, anal incontinence and rectal hypersensitivity often related to altered rectal compliance (Rasmussen *et al.*, 1990, Chan *et al.*, 2005a); in such individuals, sensory dysfunction is associated with increased symptom severity and reduced quality of life (Chan *et al.*, 2005c). In patients with FI and urgency, associated with hypersensitivity, upregulation of the capsaicin sensitive vanilloid receptor TRPV1 has been reported (Chan *et al.*, 2003a). Rectal hypersensitivity may improve with neuromodulation therapy, which corresponds with symptomatic improvement (Vaizey *et al.*, 1999b). The role of rectal hyposensitivity, in contrast, has been neglected although it has been hypothesised that incontinence in this setting may be secondary to either alterations of RAIR (sphincter relaxation may occur prior to cortical awareness of sensation (Remes-Troche *et al.*, 2010)) or due to faecal overflow related to primary faecal impaction (Nurko and Scott, 2011).

8.3 Part C: Rectal hyposensitivity (RH)

8.3.1 Definition of RH

Rectal hyposensitivity is defined as diminished sensation of the rectum to all modalities of stimuli. Historically, however, and for the purposes of clinical investigation, it has more practically been defined as blunted sensation to mechanical distension reflected by elevated sensory thresholds to simple balloon distension. Defining normal visceral sensation via this technique is complex. While balloon distension, due to its simplicity of execution, is generally employed clinically, it is not without criticism. Sensory responses to latex balloon distension are influenced by rate and technique of distension, distending material (i.e. air vs. water), bio-elastic properties of the rectum and location of the balloon in the rectum (Scott and Gladman, 2008). Generally, RH is detected clinically when sensory thresholds to simple latex balloon distension with a hand-held syringe are elevated beyond the normal range (Scott and Gladman, 2008) as defined as greater than two standard deviations of the mean of healthy volunteer data (Gladman *et al.*, 2003a) (see Chapter 3). However, as there is often considerable heterogeneity of testing protocols between units, normal ranges frequently differ between institutions. Gastrointestinal physiology units must therefore establish robust normal data before patients can be effectively evaluated (Scott and Gladman, 2008). Such heterogeneity has made determination of the clinical implications of RH difficult to establish. More precise assessment of visceral sensory function can be made with a

computer-controlled barostat, which has the added advantage of providing information as to the biomechanical properties of the gut wall (Whitehead and Delvaux, 1997). There are two main techniques utilized to determine rectal sensory function: 1) sensory thresholds and 2) stimulus intensity assessments. The sensory threshold protocol involves gradual distension of the bowel with an infinitely compliant balloon using stepwise increases in pressure. In a similar manner to latex balloon distension, the subject is asked to report when the first constant sensation, urge threshold and maximal tolerable intensity are experienced. Hyposensitivity is diagnosed when the pressure / volumes required for distension is elevated in comparison to the normal population (Cremonini *et al.*, 2005, Scott and Gladman, 2008). In contrast, the stimulus intensity technique instead involves distention of the rectum to a random program of standardised pressures, with the subject asked to rate intensity of sensation using a visual analog scale (VAS) (Whitehead and Delvaux, 1997, Steens *et al.*, 2002, Gladman *et al.*, 2005). In this setting, hyposensitivity is diagnosed when the subject reports VAS values below that of the normal range (Scott and Gladman, 2008) for pressure. While barostat sensory testing is considered the “gold standard” for the diagnosis of sensory dysfunction, its expense and more time consuming nature has limited its clinical use.

Rectal hyposensitivity, as defined above, is associated with altered reflex anorectal sensorimotor function. Subjects with RH require higher distension volumes to initiate anorectal reflexes such as the Rectoanal

inhibitory response (RAIR) (Remes-Troche *et al.*, 2010) and although hyposensitive patients have a “sensorimotor response” at a similar volume of distension as healthy individuals, in a high proportion (43%) this occurred in the absence of rectal sensory perception (Remes-Troche *et al.*, 2010). Rectal sensation, but not wall compliance, is affected by patient age and sex, with older patients and males requiring higher distension volumes (Lagier *et al.*, 1999, Sloots *et al.*, 2000) to reach standardised sensory thresholds.

8.3.2 Possible causes for the clinical finding of RH

8.3.2.1 Anatomical megarectum

An overly capacious rectum (anatomical megarectum) is found in 16% of patients with RH (Gladman *et al.*, 2009) presenting with a functional hindgut disorder; this can be the cause of a false positive result to balloon distension, as increased volumes of air are required to oppose the rectal wall and elicit rectal distension. Nevertheless, a significant proportion (29%) of patients with megarectum also have blunted sensation to mucosal electrical stimulation, suggesting that abnormalities in afferent processing may be related (Gladman *et al.*, 2009).

8.3.2.2 Increased compliance

Compliance is defined as the volume response to an imposed pressure and is a measure of the elasticity of the organ under study. It is the change

of volume required for each increment of pressure increase ($\Delta V/\Delta P$) (Fox *et al.*, 2006), and is generally measured with a barostat (see Chapter 10). Approximately 50% of patients with RH have hypercompliance (overdistensibility) of the rectum (Gladman *et al.*, 2009). Thus in the same way that an anatomical megarectum can be responsible for a false positive finding of apparent rectal hyposensitivity, so can an overly compliant (lax) rectum. Again, however, a significant proportion (39%) of patients with increased rectal compliance also have altered mucosal sensitivity (Gladman *et al.*, 2009), suggesting a co-existent afferent abnormality. Whether afferent dysfunction is caused by, or an effect of, biomechanical change is unknown.

8.3.2.3 Afferent nerve defect

Over one half of patients with rectal hyposensitivity appear to have true afferent nerve dysfunction, either in isolation or associated with altered rectal wall biomechanics, as discussed above (Gladman *et al.*, 2005).

Further support for this concept comes from evidence (Speakman *et al.*, 1993, Loening-Baucke and Yamada, 1995, Kubota *et al.*, 1997, Vasudevan *et al.*, 2007) of a prolongation of anal evoked potentials and an impairment of rectal mucosal electro-sensitivity and anal sensitivity occurring in constipated patients in general. Assessment of afferent function using visceral or rectal evoked potentials (EPs), however, has not been tested in subgroups of patients on the basis of sensory function /

dysfunction and the one study examining rectal evoked potentials in patients with constipation was unable to record reproducible traces in both patients and controls (Speakman *et al.*, 1993) meaning direct assessment of the rectal afferent function has not yet been adequately tested. Fortunately, more recent studies in healthy individuals and patients with IBS (Garvin *et al.*, 2010, Arebi *et al.*, 2011, Remes-Troche *et al.*, 2011) have shown that rectal EP's are reliable and reproducible measures of sensory function, and warrant reapplication in constipated patients.

8.3.2.4 Alteration in sensory processing

High rates of depression, alexithymia and somatization have been found in patients with functional gastrointestinal disorders (Addolorato *et al.*, 2008), and it has been hypothesised that this modulates cortical processing of sensation. Indeed, it is recognised that patients with depression have higher pain detection thresholds (Dickens *et al.*, 2003) than non-depressed patients, and individuals with alexithymia show altered patterns of brain activity in response to visceral stimulation (Kano *et al.*, 2007). This suggests that the presence of affective disorders or specific personality traits may directly impact on the way in which sensation is perceived by the nervous system. This has been extensively investigated in patients with hypersensitivity and irritable bowel syndrome, where experimentally induced psychological stress has been shown to influence rectal sensation (Geeraerts *et al.*, 2008). Psychological intervention has also been shown to improve sensory thresholds with a resultant improvement in bowel

symptoms (Guthrie *et al.*, 2004). In contrast, only a handful of studies exist examining such mechanisms in constipation (Wald *et al.*, 1989, Grotz *et al.*, 1994). Such studies show conflicting outcomes in regards to the role that psychological processing has on sensory dysfunction. Recently, however, RH has been shown, in a small number of patients, to be associated with an elevated global severity index and a trend towards depression (Lee and Lee, 2013).

8.4 Part D: Rectal sensation and neurological disorders

8.4.1 Disorders of the peripheral nerves

While RH was first noted in patients with acquired peripheral nerve dysfunction (anaesthetic induced), there is limited understanding as to the impact of peripheral nerve disorders on the development of hindgut dysfunction, although sacrifice of the sacral nerves is known to result in loss of the urge to defaecate with subsequent constipation (Nakai *et al.*, 2000). Pelvic nerve damage secondary to obstetric injury, surgery or chronic straining at stool has been proposed to be a potential factor in the development of RH (Burgell and Scott, 2012) and hindgut dysfunction (Snooks *et al.*, 1984), however primary afferent dysfunction in patients with RH is, as yet, to be confirmed by experimental studies.

8.4.2 Disorders of the spinal cord

Almost 95% of patients with damage to the spinal cord report constipation and 75% note faecal incontinence (Krogh *et al.*, 2001). Over 80% of such patients, note an absent or abnormal defaecatory urge (Krogh *et al.*, 1997). RH has been found in up to 78% of patients with complete spinal cord injury and hindgut dysfunction, and up to 43% of individuals with incomplete lesions (Greving *et al.*, 1998, Lynch *et al.*, 2000, Pannek *et al.*, 2001). Patients with spinal cord damage present with two main syndromes (Figure 8): those with supraconal lesions (above L2) have damage to the

inhibitory sympathetic fibers and thus present with RH, but with a “hyperreflexive” rectum (with increased rectal tone and strong rectal contractions) and a pronounced RAIR (Chung and Emmanuel, 2006). In such patients, anal resting pressures are reduced (Krogh *et al.*, 2002). More importantly, there is loss of voluntary control and often an inability for the external anal sphincter to relax during defaecation (MacDonagh *et al.*, 1992) however defaecation can be triggered reflexively (Chung and Emmanuel, 2006, Furness, 2012). Patients with cauda equina lesions also have RH, but in contrast, tend to present more with a flaccid rectum due to loss of parasympathetic function. They may have reduced anal sphincter function due to overstimulation of the RAIR as a result of faecal impaction (Krogh and Christensen, 2009) and loss of parasympathic modulation (Chung and Emmanuel, 2006) but studies have also shown inherently normal internal sphincter function (Krogh *et al.*, 2002). With both complete supraconal or cauda equine lesions voluntary control of defaecation and voluntary control of the external anal sphincter is lost (Krogh and Christensen, 2009). The completeness of the spinal cord lesion also strongly influences the severity of presentation (Krogh *et al.*, 2001).

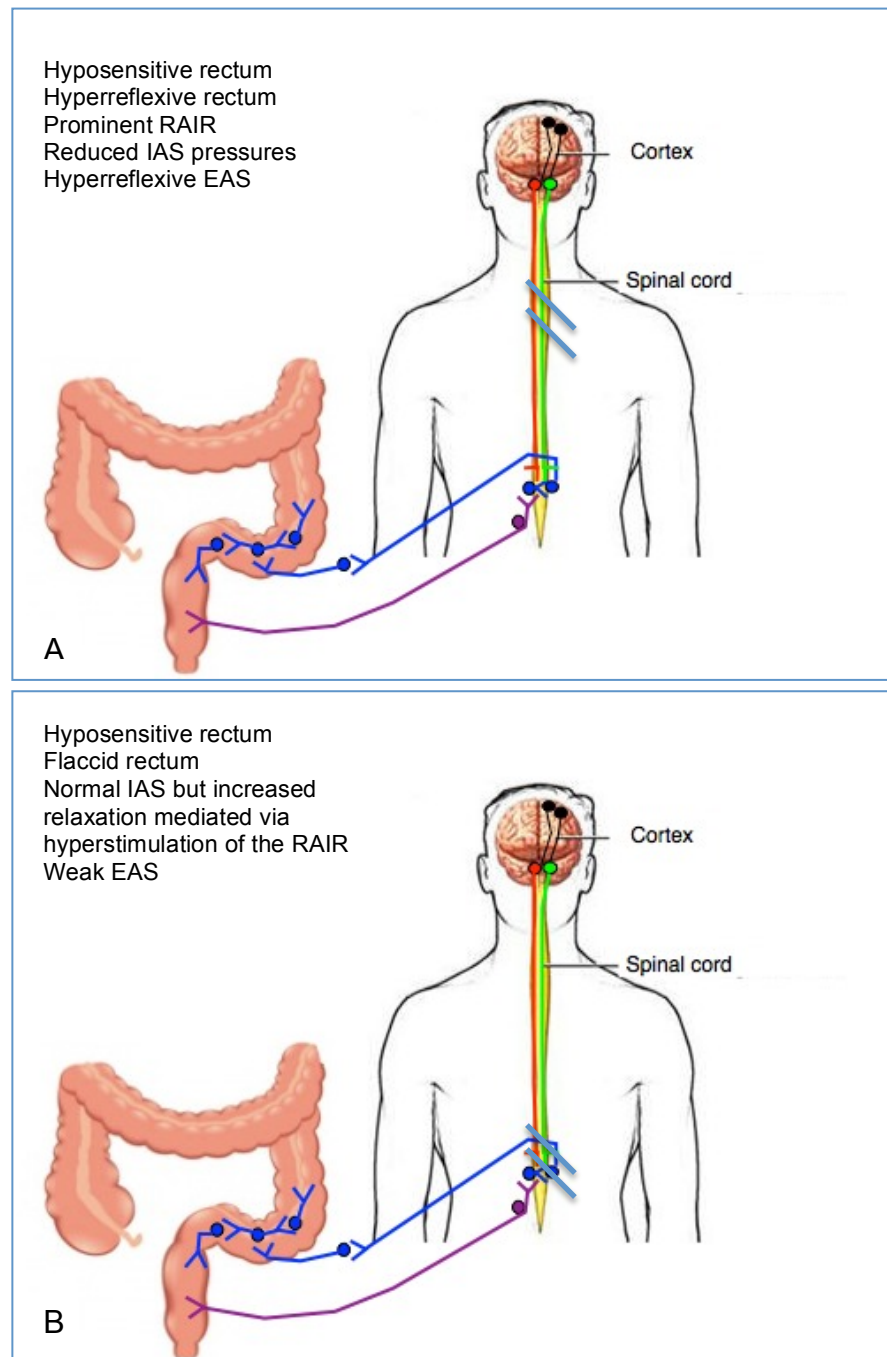


FIGURE 8 – ANORECTAL FUNCTION IN PATIENTS WITH SPINAL CORD INJURY.

(A) FEATURES ASSOCIATED WITH A SUPRACONAL SPINAL CORD INJURY;

(B) FEATURES ASSOCIATED WITH A CAUDA EQUINA SPINAL CORD LESION.

8.4.3 Systemic neurological disorders

Although rectal hyposensitivity has been predominantly described in patients with spinal cord disorders, studies have also shown that patients with systemic neurological disorders are also affected (Caruana *et al.*, 1991, Bassotti *et al.*, 1994, Nordenbo *et al.*, 1996). Such conditions are also known to be associated with hindgut dysfunction, frequently presenting with constipation.

8.4.3.1 Parkinson's disease

Up to 70% of patients with Parkinson's disease describe constipation (Rao *et al.*, 2002), and recent studies show that, onset of constipation can be an early predictor of the disease in men (Abbott *et al.*, 2001). The pathophysiology of gastrointestinal dysfunction in Parkinson's is thought to be mediated via both central and peripheral pathways with the enteric nervous system affected at an earlier stage of the disease (Ismail *et al.*, 2009). Although the predominant physiological abnormalities in such patients include paroxysmal contraction of puborectalis and abnormal sphincter function (Clarke *et al.*, 2012), rectal hyposensitivity has also been found in some studies to be a feature (Ricciardi *et al.*, 2006). However, the clinical significance of sensory dysfunction in such patients remains unclear.

8.4.3.2 Multiple sclerosis (MS)

MS patients tend to present with a picture that is a mix of those associated with supraconal and conal lesions of the spinal cord (Krogh *et al.*, 2001). Two-thirds of patients describe hindgut dysfunction with almost 50% reporting constipation (Hinds *et al.*, 1990, Munteis *et al.*, 2006). Bowel dysfunction, like bladder dysfunction, seems to be particularly an issue in patients with spinal cord disease in comparison to those with cortical lesions (Preziosi *et al.*, 2013). Patients with MS may have decreased sphincter squeeze and resting pressures as well as rectal hyposensitivity; a finding that correlates well with the presence of faecal incontinence (Caruana *et al.*, 1991, Nordenbo *et al.*, 1996).

8.4.3.3 Diabetes

Up to 30% of patients with diabetes describe constipation (Abbott *et al.*, 2001) and almost 20% note incontinence (Amaral *et al.*, 1997). Patients with faecal incontinence associated with diabetes have been shown to have higher rectal sensory thresholds than those with incontinence in the absence of diabetes (Wald and Tunuguntla, 1984, Caruana *et al.*, 1991). Rectal sensation does not appear to be influenced by hyperglycaemia *per se* (Russo *et al.*, 2004), suggesting chronic neuropathy is the underlying pathology. Indeed, in diabetic patients with upper gut dysfunction associated with visceral hyposensitivity, direct assessment of the afferent pathways with cortical evoked potentials found abnormalities of neuronal transmission in patients but not controls (Rathmann *et al.*, 1991, Kamath

et al., 1998). Subsequent animal studies in diabetic rats have shown that diabetic neuropathy predominantly affects the low threshold mechanoreceptors, commonly responsible for the awareness of physiological stimuli (i.e. the urge to defaecate) (Beyak *et al.*, 2009). Importantly, rectal sensation in such patients can be modulated by sensory-directed biofeedback with resultant improvement in symptoms (Wald and Tunuguntla, 1984).

8.5 Part E: The importance of rectal hyposensitivity in functional hindgut disorders

8.5.1 Current understanding of RH and hindgut dysfunction

Rectal hyposensitivity has been found in 23% of adult patients with constipation, 10% of patients with faecal incontinence and 27% of patients with a co-existence of both (Gladman *et al.*, 2003a); however the true clinical significance of this finding is yet to be determined. In many patients, RH may be the only discernible abnormality on thorough physiological assessment (Gladman *et al.*, 2003a). Therapies targeted at rectal sensory function have been found, in a number of conditions, to result in improvement in symptoms (Rao *et al.*, 1997, Williams *et al.*, 2000, Lee *et al.*, 2006, Knowles *et al.*, 2012), indicating that RH is clearly important in the pathogenesis of hindgut disorders: However, the magnitude of its impact is, as yet, unknown.

Bowel retraining therapy, often incorporating sensory biofeedback is frequently used for the management of constipation and rectal evacuatory dysfunction (Peticca and Pescatori, 2002, Gladman *et al.*, 2006, Scott and Lunniss, 2011, Rao, 2011). Enhancement of sensory perception is one of the primary aims of therapy (Rao, 2011). Biofeedback has been shown to both objectively (up to 92% of patients show a significant improvement in sensory thresholds following treatment (Snooks *et al.*, 1984, Rao *et al.*,

1997, Peticca and Pescatori, 2002) and subjectively improve symptoms of constipation (Rao *et al.*, 1997, Mollen *et al.*, 1999, Peticca and Pescatori, 2002) and incontinence (Wald and Tunuguntla, 1984, Snooks *et al.*, 1984), with sustained improvement for at least 12 months (Ozturk *et al.*, 2004). Unfortunately, studies have also shown that those with the most marked elevation of rectal sensory thresholds are more likely to fail such therapies (Snooks *et al.*, 1984, Connor *et al.*, 2009, Firestone Baum *et al.*, 2013).

Neuromodulation therapy, involving modulation of the extrinsic neural control of the pelvic floor via continuous low amplitude stimulation of the sacral nerve roots or via direct stimulation of the organ of interest (i.e. anal canal), has also been hypothesised to act via alteration of sensory pathways. Sacral nerve stimulation has been shown to result in normalization of rectal sensory thresholds with treatment, associated with both an increase in the number of successful bowel actions, and also improved constipation symptom scores (Kamm *et al.*, 2010, Knowles *et al.*, 2012), suggesting a possible mechanistic effect of RH. Magnetic sacral nerve stimulation has also shown that symptomatic benefit is associated with a significant decrease in rectal sensory volumes to urge to defaecate and maximal toleration (Lee *et al.*, 2006). Importantly, in this study, baseline rectal sensory status also predicted response to therapy. As a group, responders had significantly higher baseline sensory thresholds (maximal tolerable volume 296 ml vs. 143 ml) (Lee *et al.*, 2006) in comparison to the non-responders.

Less invasive electrical stimulation techniques have also been trialed and are likewise found to influence rectal sensory status (Chang *et al.*, 2003, Chang *et al.*, 2004) allied to symptomatic improvement. More recently, transcutaneous abdominal electrical stimulation and dorsal genital nerve stimulation have been trialed in children and adults respectively, with an improvement in constipation symptoms and rectal perception again shown (Leong *et al.*, 2011, Worsoe *et al.*, 2012).

The presence of rectal hyposensitivity has also been shown to negatively effect treatment outcomes for surgical interventions in patients with constipation (Sood *et al.*, 2002, Di Lorenzo *et al.*, 2002). Whether this is due to a direct effect, or rather because sensory dysfunction is a marker for a more severe clinical phenotype is unclear.

Anecdotally, it is often noted that patients with chronic constipation and RH describe an attenuated, altered or absent call to stool and this has been confirmed in at least one study (Harraf *et al.*, 1998). Such patients may describe lower abdominal pain or cramping as the stimulus for defecation in contrast to those with normal sensation, who appear to associate the call to stool with a sensation of rectal filling. While these observations from clinical care raise interesting questions, whether such an alteration in “defaecatory urge” truly exists in such patients has not been formally examined. Clinical experience (unpublished – authors observation) also suggests that patients with RH often seem to describe

more severe symptoms than patients with normal sensation, and may be more likely to fail established therapies (Di Lorenzo *et al.*, 2002, Connor *et al.*, 2009, Firestone Baum *et al.*, 2013), however this has never been systematically studied.

There is emerging evidence to suggest that there may be a definable clinical phenotype for RH. For instance, rectal hyposensitivity is rarely associated with mechanical anorectal obstruction (Wijffels *et al.*, 2011), but rather functional causes of evacuatory abnormalities (Gladman *et al.*, 2003b) such as dyssynergic defaecation. Early studies have shown that almost 50% of patients with RH have features of functional obstruction (Gladman *et al.*, 2003b) on proctography or anorectal manometry. The possible association of sensory (RH) and motor (functional evacuatory disorder) suggests a possible neuropathic process, affecting both sensory and motor neurons, (i.e. pelvic nerve damage) may underlie symptoms of hindgut dysfunction in such patients. However, the overall association of sensory and motor dysfunction in constipated patients has recently been questioned (Lee *et al.*, 2013) as, although functional defaecatory disorders are commonly seen in patients with sensory dysfunction, they do not appear to be significantly associated. This may reflect, however, the poor concordance between tests (Palit *et al.*, 2012b) used to identify dyssynergia rather than a true lack of association.

8.5.2 Gaps in current understanding of RH and hindgut dysfunction

While the association between functional hindgut disorders and RH is well established, there is limited understanding as to the role that RH plays in symptom generation. In short, the clinical significance of the physiological finding remains unknown. Whether RH impacts upon clinical presentation, symptoms duration / chronicity or perhaps severity of the condition, has not been adequately established.

There is also understanding of the influence of RH on faecal incontinence. Although commonly associated, occurring in 10% of patients with FI alone and over one-quarter of patients with FI and constipation, RH has been relatively relegated in favour of studies focusing on rectal hypersensitivity in FI. Rectal hypersensitivity in such patients may be a learnt response to an incompetent sphincter and it is thus possible that the high prevalence (44%) of rectal hypersensitivity seen in women with incontinence (Chan *et al.*, 2005c) is confounded by the presence of sphincter defects. The true impact of RH in patients with FI may therefore be underestimated.

Pioneering studies in patients with faecal incontinence and to a lesser extent constipation suggest that RH maybe a marker for occult spinal cord injury (Varma and Smith, 1988, Sun *et al.*, 1990a, Sun *et al.*, 1992). In patients in whom there is documented disruption of the afferent pathway (e.g. due to pelvic nerve damage or spinal cord injury), the cause-effect

relationship to the development of RH appears clear cut. However, the role that sub-clinical systemic neuronal dysfunction plays in the development of RH is less clear. Damage to the pelvic nerves either during childbirth (Snooks *et al.*, 1986), due to chronic straining at stool (Lubowski *et al.*, 1988), or due to pelvic surgery (particularly hysterectomy) has also been postulated as a cause (Gladman *et al.*, 2003b, Scott and Lunniss, 2011). Nevertheless, the level at which neuronal pathway dysfunction occurs in individuals with RH remains to be elucidated. Interestingly, such patients appear to have intact spinal reflexes (RAIR, recto-anal contractile response) albeit requiring elevated distension volumes to induce the response (Remes-Troche *et al.*, 2010). This suggests any potential abnormality may be above the level of the reflex arc. Furthermore, evidence, predominantly from studies of patients with hypersensitivity and functional bowel disorders, also suggests that rectal sensory function may also be influenced by personality profile, autonomic nervous system function and psychological phenotype (Sarkar *et al.*, 2000, Hobson *et al.*, 2006, Paine *et al.*, 2009, Coen *et al.*, 2011, Botha *et al.*, 2011). Whether the same holds true for patients with hyposensitivity remains to be confirmed.

Ultimately, the underlying abnormality responsible for the finding of rectal hyposensitivity has not been confidently established. In particular, the *site* or the *extent* of the proposed disruption to the afferent nerve pathway has not been elucidated nor has the pathology leading to biomechanical rectal

wall changes been adequately explained. Whether the proposed afferent nerve defect is an isolated finding or combined with changes in efferent or autonomic function remains unclear. More importantly, the clinical impact of rectal hyposensitivity still remains to be defined.

9 THESIS HYPOTHESES AND OVERVIEW

9.1 Part A: General Hypotheses

9.1.1 Clinical implications of rectal hyposensitivity

Rectal hyposensitivity (RH) has been shown to be associated with chronic constipation, coexistent faecal incontinence and constipation and, to a lesser extent, faecal incontinence in isolation. Whether RH is associated with increased severity or specific patterns of symptoms in functional hindgut dysfunction is as yet unknown. ***It is hypothesised that rectal hyposensitivity is associated with increased severity scores, as well as specific symptom patterns and alteration in urge to defaecate in patients with faecal incontinence and chronic constipation.***

9.1.2 Pathophysiology of rectal hyposensitivity.

Afferent nerve dysfunction has been proposed as a likely cause of RH. Disruption at any point within the delicate network of nerves from the receptor level in the bowel wall to the higher centres of the brain may potentially result in disordered sensing of stimuli in the gastrointestinal tract. ***It is hypothesised that isolated dysfunction of the afferent nerve pathway is a cause for the physiological finding of rectal hyposensitivity.***

9.2 Part B: Specific research questions

9.2.1 Clinical implications

1. Is RH a predictor of symptom severity in patients with chronic constipation and faecal incontinence?
2. Is the presence of RH associated with specific symptoms of constipation?
3. In the absence of sphincter incompetence (i.e. obstetric injury) in faecal incontinence, is RH allied to the presence of co-existent constipation?
4. Is the presence of RH associated with specific changes in patterns of sensation associated with the urge to defaecate?

9.2.2 Physiological implication

1. Can objective measure of the transmission of visceral sensory information confirm dysfunction of the afferent pathway?
2. Is there evidence of alteration in cortical processing of rectal stimuli in patients with rectal hyposensitivity in comparison to healthy individuals?
3. Is there evidence of sensorimotor neuronal dysfunction as suggested by co-existent efferent neuronal abnormalities in patients with rectal hyposensitivity?
4. Is the afferent defect isolated to the viscera, or does it affect both somatic and visceral nerves?

9.3 Part C: Thesis overview

The introduction to this thesis will focus on prior background knowledge of the association between rectal hyposensitivity and constipation and faecal incontinence. In particular, these disorders will be defined and the difficulties with sub-classification identified. The neuronal pathways governing control of the hindgut will be explored in detail, and the current understanding of rectal hyposensitivity and its association with hindgut dysfunction and neurological disturbance will be summarised. Established investigations and research tools used in the study of constipation will be discussed.

The major body of work of this thesis examines the clinical impact of RH in patients with constipation and incontinence, including reporting of what patients perceive as their prompt to defaecate or “call to stool”. To date, this has not been well established, in part due to the confusing and often arbitrary sub-classifications and nomenclature used in the stratification of patients with hindgut dysfunction.

The subsequent sections are physiologically based, and aim to determine whether a true afferent neuronal defect is responsible for the development of RH. The function of the afferent pathway will be examined from the cortex to the periphery in an attempt to identify the site of dysfunction.

Cortical processing will be studied by determining the source of cortical evoked potentials generated in response to sensory stimuli using an inverse modelling technique. Furthermore, peripheral and spinal transmission will be assessed by comparing the general latency and amplitude of evoked potentials in response to rectal stimuli.

Finally, whether other neuronal pathways are affected will be examined, including efferent and somatic systems. This will improve understanding of the nervous system control of the rectum, as well as the mechanisms involved in the process of normal or abnormal defaecation.

This thesis will conclude with suggestions for future research, to address questions raised from the results of studies performed here within.

10 METHODS

10.1 Part A: Ethics and regulatory approvals

10.1.1 Epidemiological studies

Chapter 11 & 12

All data accrued for studies undertaken in Chapter 11 and 12 were collected as part of routine clinical assessment of patients seen in the GI Physiology Unit of Bart's Health trust, London and was analysed anonymously as part of a clinical audit.

Chapter 13

Patient information was obtained from an audit of data obtained following routine clinical assessment of patients presenting to the Bart's Health trust GI Physiology Unit for investigation of constipation. All the data was analysed anonymously. Healthy volunteer data was obtained from a study running concurrently within the Wingate institute of Neurogastroenterology, approved via Queen Mary University London Ethics Committee (REC number: QMREC 2012/13).

10.1.2 Physiology studies

Chapter 14 & 15

The experimental protocols were approved by the East London and the City Alpha Research Ethics Committee (REC number. 10/H0704/11).

10.2 Part B: Study population

10.2.1 Epidemiological studies

Chapter 11.

This was a retrospective audit of prospectively collected data obtained during the clinical assessment of consecutive patients presenting to the GI Physiology Unit for investigation of functional hindgut disorders over a ten year period (2003 – 2012). Patients were included if they had adequately completed a comprehensive history questionnaire, routinely utilised in clinical practice, and had undergone rectal sensory testing with simple latex balloon distension as part of their investigative work-up.

Chapter 12.

Males with faecal incontinence were selected from the above data set. Patients were included if, following manual review by the investigator, data for both the clinical symptom questionnaires and standard anorectal physiological investigations, including rectal sensory testing and proctography, were complete.

Chapter 13.

Female patients presenting for assessment of symptoms of chronic constipation over a 12 month period (2012) completed a viscerosensory questionnaire (see Chapter 13 for details) used in the routine assessment of such patients. Patients were included if, following manual review by the

investigator, data for the questionnaire was complete and rectal sensory threshold data were available.

10.2.2 Physiological experiments

10.2.2.1 Inclusion criteria

10.2.2.1.1 *Healthy volunteers*

1. no history of gastrointestinal disease or symptoms of hindgut dysfunction
2. normal rectal sensory thresholds to balloon distension (see below)

10.2.2.1.2 *Patients with chronic constipation and rectal hyposensitivity*

1. defined as unsatisfactory defaecation characterized by infrequent stools, difficult stool passage or both, at least for the previous three months and where appropriate investigations have occurred and a secondary cause excluded
2. as determined by elevated sensory thresholds to balloon distension (see below)

10.2.2.1.3 Patients with chronic constipation and normal rectal sensation

1. constipation (defined as above)
2. defined by normal sensory thresholds to balloon distension testing (see below).

10.2.2.2 Exclusion criteria

- inability to provide informed consent for the research study
- neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease
- previous spinal surgery, or documented spinal injuries including spinal cord transection
- congenital anorectal anomalies or absence of native rectum due to surgery
- external full thickness rectal prolapse
- previous rectal surgery
- stoma *in situ*
- chronic bowel diseases such as inflammatory bowel disease
- epilepsy or cranial implants
- pregnancy or intention to become pregnant

10.3 Part C: Clinical tests for the investigation of chronic constipation

Several routine clinical diagnostic tests were employed to assess colonic and anorectal function in the study cohorts

10.3.1 Examination of rectal sensitivity

10.3.1.1 Latex balloon distension

(Chapter 11, 12, 13, 14, 15)

Subjects examined in these studies were classified into one of three categories by rectal latex balloon distension (Figure 9): (i) normal rectal sensation, (ii) rectal hypersensitivity, or (iii) rectal hyposensitivity (RH). Three sensory thresholds were determined via ramp distension of a simple latex balloon, connected to a Foley catheter and positioned 10 cm from the anal verge, with air at 1 ml/sec: first constant sensation (upper limit of normal 150 ml [male] / 110 ml [female]), defaecatory desire volume (upper limit of normal 190 ml [male] / 200 ml [female]) and maximal tolerable volume (lower limit of normal 80 ml [both sexes], upper limit of normal 320 ml [male] / 300 ml [female]).

Normative data was previously derived from 91 healthy subjects (unpublished, Table 3) assessed within the GI Physiology Unit. Normal reference ranges were established based on two standard deviations above the mean of healthy control data as used previously (Gladman *et al.*,

2003a, Gladman *et al.*, 2003b, Gladman *et al.*, 2005, Gladman *et al.*, 2009, Vasudevan *et al.*, 2007). Two standard deviations from the mean was used to define the upper limit of normal within this thesis to maintain consistency with previously published studies. However, it is appreciated that alternative definitions may be used to define normality and this may provide alternative values. For example, linear regression techniques using constipation severity scores to determine clinically significant normal ranges would be ideal. However, as the clinical impact of sensory dysfunction is unknown, this form of analysis has not yet been able to be performed. In addition, the majority of patients with hindgut dysfunction also have sensory thresholds within the ranges seen in healthy individuals, most likely reflecting the variable pathogenic mechanisms responsible for the clinical finding of constipation. Such heterogeneity limits the use of other techniques for determining clinically significant reference ranges such as ROC curves. Therefore, for this thesis, and in line with published research within this field, the use of a statistically determined normal range based on the physiology of health was felt to be most appropriate.

TABLE 3 – DEMOGRAPHICS (AGE, PARITY) AND NORMAL RANGES OF SENSORY THRESHOLDS IN HEALTHY VOLUNTEERS

	Males N = 41	Females N = 50
Age	Mean 36 (range 21 – 58)	Median 43 (range 18 – 63)
Parity	N/A	Median 1 (range 0 – 4)

FCS		
Mean	50 ml	30 ml
+/- 2SD	15 – 150ml	20 – 110 ml
DDV		
Mean	115 ml	85 ml
+/- 2SD	40 – 190 ml	40 – 200 ml
MTV		
Mean	200 ml	150 ml
+/- 2SD	75 – 320 ml	75 – 290 ml



FIGURE 9 – EQUIPMENT REQUIRED FOR PERFORMING LATEX BALLOON DISTENSION OF THE RECTUM.

The retest reliability of latex balloon measures has been examined in a number of studies. In the largest study, Chan *et al* performed repeated sensory thresholds to balloon distension in 31 healthy volunteers and excellent agreement was found between studies performed 4 weeks apart (Chan *et al.*, 2003b). Minimal inter-individual variability has been found in patients with hindgut dysfunction (irritable bowel syndrome) undergoing balloon sensory testing on separate occasions (Prior *et al.*, 1990). Although there are studies, albeit with significantly smaller sample sizes ($n = 6$), which have shown more heterogeneous results (Goke *et al.*, 1992).

A smaller number of studies have attempted to address which rectal sensory threshold is most valid. Maximal tolerable sensation is considered most robust (Varma and Smith, 1986, Sorensen *et al.*, 1992, Rasmussen, 1994) with first threshold and urge threshold found to be more subjective. Unfortunately, the small sample size (maximum $n = 15$) of such studies limits the strength with which conclusions can be drawn. Intuitively, defaecatory urge threshold would seem most clinically important but this has not been examined definitively.

10.3.1.1.1 Limitations

Latex balloon distension, though recommended as the first-line assessment of rectal sensation in routine clinical practice (Scott and Gladman, 2008), is confounded by the elastic recoil properties / intrinsic compliance of the balloon itself. In the presence of elevated sensory

thresholds, the test is, as a result, unable to distinguish between “true” afferent nerve dysfunction and hyper-compliance / dilation of the rectum (Figure 10). Consequently, the test is best considered a screening test; it inherently has high sensitivity but low specificity.

As latex balloon distension is the most prevalent clinical test to assess visceral sensitivity, it was utilised on pragmatic grounds within this thesis to define RH and allow comparison with patients’ symptom phenotype to ascertain the clinical significance of RH. However, given the limitations described above, where more precise measures of afferent function were required, including assessment of bio-elastic properties of the rectum (Chapter 15), Barostat assessment of rectal sensitivity and compliance was employed (see section 10.4.1).

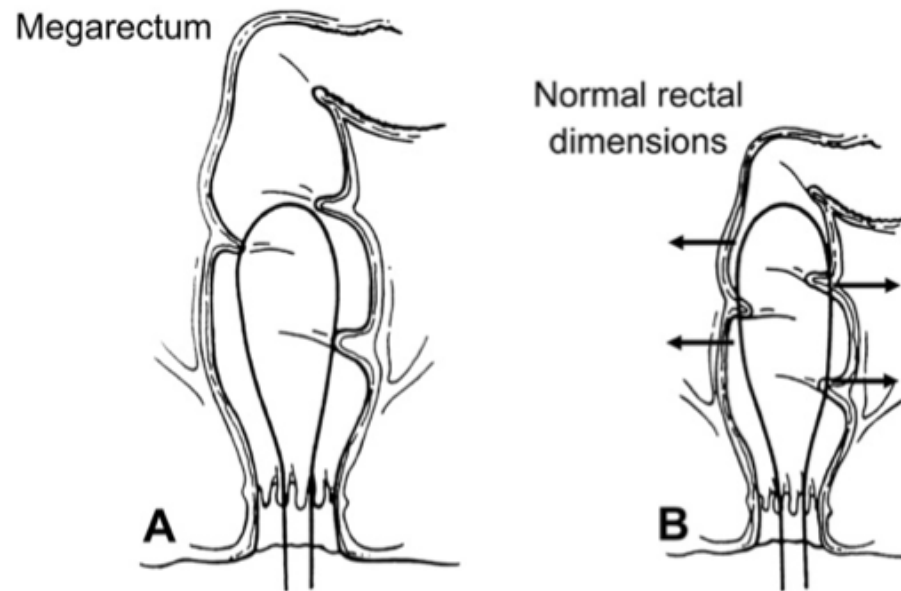


FIGURE 10 – THE EFFECT OF RECTAL BIOVISCOELASTIC OR MECHANICAL PROPERTIES OR DIMENSION ON THE RESULTS OF LATEX BALLOON DISTENSION

(A) AN OVERLY CAPACIOUS OR COMPLIANT RECTUM REQUIRES A LARGER VOLUME TO INDUCE RECTAL DISTENSION THAN THAT REQUIRED IN NORMAL RECTUM (B). REPRODUCED FROM (SCOTT *ET AL.*, 2011) WITH PERMISSION FROM ELSEVIER

10.3.2 Examination of colonic function

10.3.2.1 Radio-opaque marker study

(Chapter 14 & 15)

A radio-opaque marker (ROM) study is a surrogate measure of colonic transit and an indirect measure of colonic motility. The patient ingests a gelatine capsule, containing a number of ROMs; an X-ray is taken a standard time later, and the number of markers retained within the colon is determined. There are a number of different protocols in use worldwide; the simplest method involves ingesting 50 markers with the abdominopelvic X-ray performed at 100 hours. In this protocol > 20% of markers retained is considered abnormal (Dinning *et al.*, 2009a).



FIGURE 11 – RADIO-OPAQUE MARKER (ROM) STUDY IN A PATIENT WITH SLOW TRANSIT CONSTIPATION

REPRODUCED FROM (KROGH AND CHRISTENSEN, 2009) WITH PERMISSION FROM ELSEVIER.

10.3.2.1.1 Limitations

Classifying a marker study as a “colonic” investigation is somewhat of a misnomer as, more accurately, it is a measure of whole gut transit. Any pathology from the mouth to the anus can influence the outcome. The distribution of any retained markers within the colon is often used to indicate whether the delay is secondary to colonic inertia or outlet obstruction (Southwell *et al.*, 2009); however segmental analysis of transit

can be difficult or unreliable as primary evacuatory dysfunction may secondarily influence proximal colonic transit (Dinning *et al.*, 2005).

10.3.3 Assessment of evacuatory function

10.3.3.1 Anorectal manometry

(Chapter 12, 14 and 15)

Anorectal manometry (Figure 12) primarily allows for the assessment of internal and external anal sphincter function and determination of the presence of rectoanal reflexes. It also allows for assessment of the coordinated response of the anorectum to simulated defaecatory manoeuvres. It is performed with the patient lying in the left lateral position with knees and hips flexed (Scott and Gladman, 2008).

Basic requirements for performing this investigation are:

1. a thin intraluminal pressure-sensing catheter. In the studies presented in this thesis, a water perfused catheter was used;
2. pneumohydrolic water-perfusion system;
3. pressure transducers;
4. a rectal balloon. This may be either attached to the manometric catheter or mounted on a separate catheter (e.g. 14G Foley catheter) as utilised for rectal sensorimotor testing;
5. an amplifying-recording-display system.

The catheter is introduced through the anal canal and into the rectum. A period of familiarization allowing the recordings to stabilise is first performed. The minimum standards for reporting the results of anorectal manometry require:

- (1) measurements of maximal anal resting tone (lower limit of normal 50 cmH₂O);
- (2) maximal incremental squeeze pressures (lower limit of normal 50 cm H₂O) and;
- (3) functional anal canal length (Rao *et al.*, 2002).

In the studies within this thesis, the procedure was performed using a station pull-through technique over a 5 cm distance. Poor resting anal sphincter pressures correlates well with the presence of passive faecal incontinence (Engel *et al.*, 1995), with resting tone thought to predominantly represent internal anal sphincter function (55% - 80% of function) (Chung and Emmanuel, 2006, Krogh and Christensen, 2009) with weakness frequently attributed to disruption or degeneration of the smooth muscle sphincter (Scott and Gladman, 2008). Anal squeeze pressure, in contrast, represents predominantly external anal sphincter function and contraction of puborectalis (Scott and Gladman, 2008). However, in reality the contribution of each sphincter is likely to be less well demarcated, as patients with very low resting sphincter pressures

may be fully continent and those with normal tone, incontinent (Felt-Bersma *et al.*, 1990).

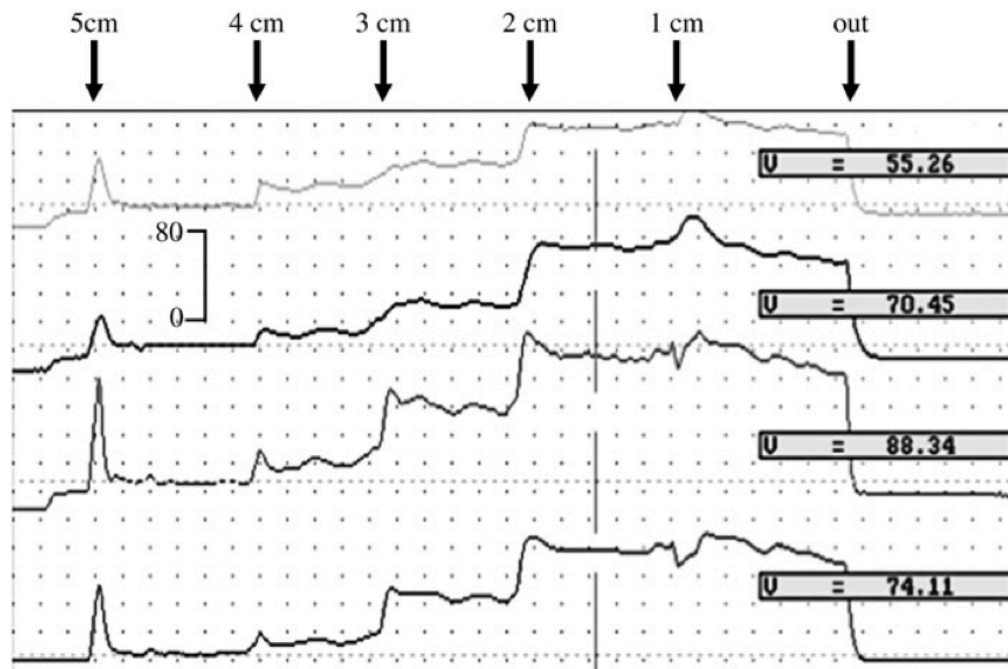


FIGURE 12 – STATION PULLED THROUGH ANAL MANOMETRY (FOUR CHANNEL RADIALLY SPACED AT 90 DEGREES) OVER A 5 CM DISTANCE

THE CATHETER IS GRADUALLY WITHDRAWN AND MEASUREMENTS TAKEN AT 1 CM SPACED STATIONS. THE FUNCTIONAL ANAL CANAL LENGTH IS CALCULATED AS THE DISTANCE OVER WHICH THE RECORDED PRESSURES ARE AT LEAST HALF THAT OF THE MAXIMAL RESTING PRESSURE OF THE ANAL CANAL (SCOTT AND GLADMAN, 2008). MAXIMAL RESTING PRESSURE IS THE HIGHEST PRESSURE OBTAINED WITHIN THE ANAL CANAL. REPRODUCED FROM (SCOTT AND GLADMAN, 2008) WITH PERMISSION FROM ELSEVIER.

Anorectal manometry also assesses sacral reflexes including the rectoanal inhibitory (RAIR) and excitatory reflexes and cough reflex. The RAIR is examined by rapidly inflating the rectal balloon (as described above) to 60 ml, mimicking the rapid arrival of stool into the rectum. In

health, the stimulus results in a transient increase in rectal pressure, then a transient increase in anal pressure (recto-anal excitatory reflex: RAER) followed by a prolonged decrease in anal pressure as a result of relaxation of the internal anal sphincter (the recto-anal inhibitory reflex: RAIR) (Figure 13). A normal RAIR induces at least a 25% reduction in anal canal pressure from resting baseline (Lowry *et al.*, 2001). If a response is not induced, the same procedure is repeated with increasing volumes of air to a maximum of maximal tolerable volume (MTV). The volume required to induce the RAIR is recorded.

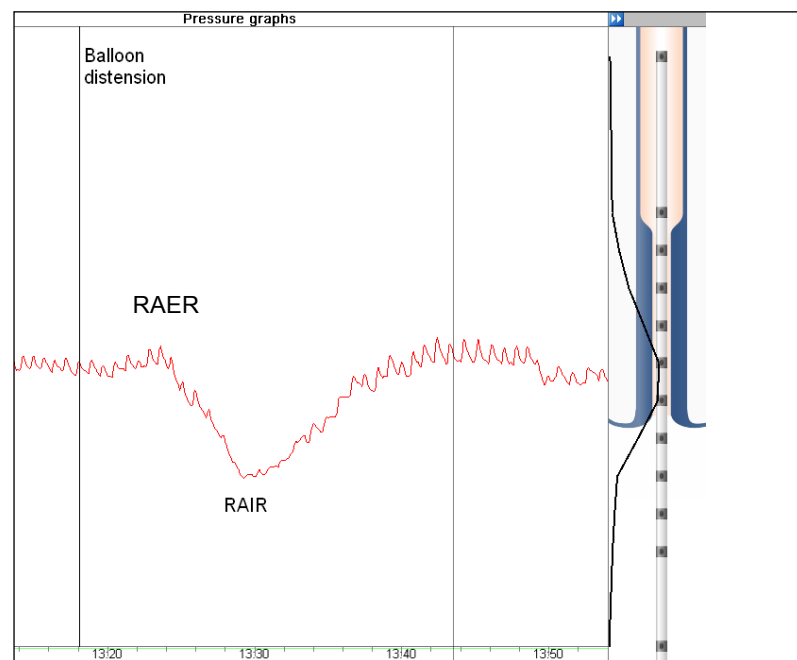


FIGURE 13 – EXAMPLE OF A MANOMETRIC RECORDING OF THE RECTOANAL EXCITORY AND INHIBITORY REFLEX IN RESPONSE TO RECTAL BALLOON DISTENSION TO 60 ML OF AIR.

NOTE THE TRANSIENT INCREASE IN SPHINCTER PRESSURE (RAER) BEFORE A PROLONGED RELAXATION (FALL IN PRESSURE) IS NOTED (RAIR)

The RAIR is an intramural reflex and is mediated via the myenteric plexus and is thus dependent on an intact enteric nervous system (Remes-Troche and Rao, 2008). The afferent components of the reflex are tension receptors in the rectal wall, pelvic floor and anorectal mucosa (Uher and Swash, 1998). It is also modulated by the descending control of the spinal cord (Krogh *et al.*, 2002). It is absent in patients with Hirschsprug's disease, following rectal myomectomy and occasionally after anterior resection (Remes-Troche and Rao, 2008). The percentage relaxation of the RAIR has also been shown to be impaired in patients with chronic constipation (Loening-Baucke and Younoszai, 1982, Xu *et al.*, 2008) and sacral / cauda equina spinal lesions (Krogh *et al.*, 2002).

The recto-anal contractile reflex induced following cough is a polysynaptic reflex (Chan *et al.*, 2004). Generally it has a higher pressure response than that achieved with voluntary squeeze (Uher and Swash, 1998).

Anorectal manometry can also be used to assess evacuatory function. By inflating a rectal balloon with 50ml of air and requesting, with the patient seated on a commode, that they attempt to expel it, provides a helpful screening test of evacuatory function. A healthy individual should be able to evacuate the balloon within approximately 50 sec (Scott and Gladman, 2008). The anal and rectal pressure profiles generated during attempts at evacuation can help determine the pattern of dyssynergia as previously

discussed (chapter 8.2.1.3.2) (Rao and Singh, 2010).

10.3.3.1.1 Limitations

While manometry is highly sensitive for detecting neuromuscular dysfunction of the sphincter complex, it provides no measure of sphincter anatomy. As a result, the test is unable to determine whether the underlying cause of such dysfunction is primarily structural or functional (such as secondarily to sphincter denervation) in origin. Interpretation of the sacral reflexes (particularly RAIR) may also be difficult in patients with low base line resting tone. Assessment of the response to defaecatory manouvers can also be influenced by patient embarrassment and position in which the examination is carried out (left lateral position is associated with over reporting of dyssynergia when compared with an examination in the seated position (Rao, 2008)). Balloon expulsion and anorectal manometry also do not exclude structural abnormalities such as rectocele, enterocele or intussusception as a cause of obstruction to defaecation. As a result, in this thesis, evacuation was assessed using proctographic methods described below.

10.3.3.2 Evacuating proctography

(Chapters 12, 14 and 15)

Proctography is a fluoroscopic examination of defaecation. It requires the introduction of a radio-opaque contrast, consisting of a defined mixture of

water, porridge and barium sulphate (neostool) to simulate a soft stool, into the rectum via a proctoscope until a strong and sustained desire to defaecate is produced. The patient is then transferred to a commode, and fluoroscopy is performed while the subject attempts to evacuate the neostool. In health, at rest, the rectum is pulled forwards by the puborectalis, an important mechanism of continence producing an angle of between 90 and 110° (Lowry *et al.*, 2001) between the posterior wall of the rectum and the anal canal. With defaecation there should be relaxation of the puborectalis muscle with resultant straightening of the anorectal angle by at least 15° with a degree (1 – 3 cm) of pelvic floor descent (Lembo and Camilleri, 2003).

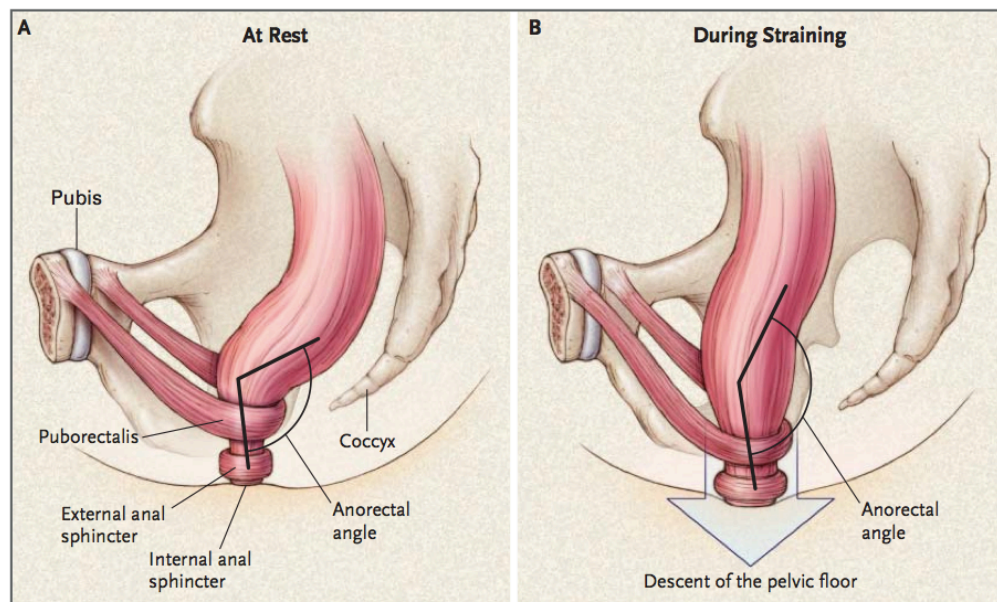


FIGURE 14 – SCHEMATIC ILLUSTRATION OF THE ANORECTUM AT REST (A) AND DURING STRAINING TO DEFAECATE (B).

AT REST, CONTINENCE IS MAINTAINED BY TONIC CONTRACTION OF BOTH THE INTERNAL SPHINCTER AND PUBORECTALIS MUSCLE (WHICH PULLS THE RECTUM FORWARDS PRODUCING THE "ANORECTAL ANGLE"). WITH DEFAECATION, RELAXATION OF THE PUBORECTALIS (AND PELVIC FLOOR MUSCLES) OCCURS

ALLOWING STRAIGHTENING OF THE RECTUM AND RELAXATION OF THE ANAL SPHINCTERS, PERMITTING THE PASSAGE OF STOOL. REPRODUCED FROM (LEMBO AND CAMILLERI, 2003) WITH PERMISSION, COPYRIGHT MASSACHUSETTS MEDICAL SOCIETY.

Proctography is a comprehensive test of evacuation, as it can distinguish between mechanical obstruction, such as secondary to an intussusception or rectocele (Figure 18, Figure 19), and functional obstruction such as that seen in dyssynergic defaecation. Dyssynergia is diagnosed by proctography when there is failure of the anal canal to open during defaecation; failure of relaxation of puborectalis (Scott and Gladman, 2008, Lunniss *et al.*, 2009), as evidenced by an inability of the anorectal angle, defined as the angle between the axis of the anal canal and distal half of the posterior rectal wall (Agachan *et al.*, 1996b) to open (become obtuse) during defaecation (Figure 15, Figure 16).

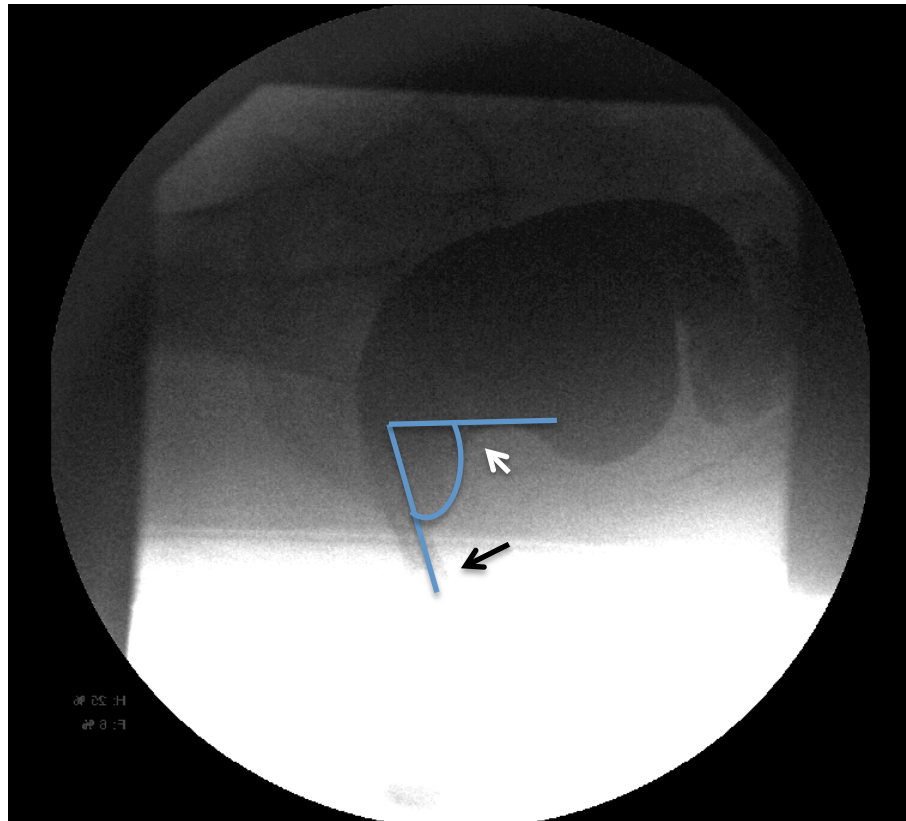


FIGURE 15 – PROCTOGRAPHIC FEATURES OF DYSSYNERGIC DEFACATION: PRE DEFACATION

IMAGE TAKEN FROM THE LEFT WITH THE PATIENT SEATED ON A COMMUNE. IN THIS IMAGE, THE CONTRAST CAN BE SEEN TO FILL THE RECTUM. THE ANAL CANAL IS OUTLINED BY A SMALL LINE OF CONTRAST (BLACK ARROW). NOTE THE ANGLE MADE BY THE ACTION OF THE PUBORECTALIS MUSCLE ON THE POSTERIOR WALL OF THE RECTUM (WHITE ARROW).

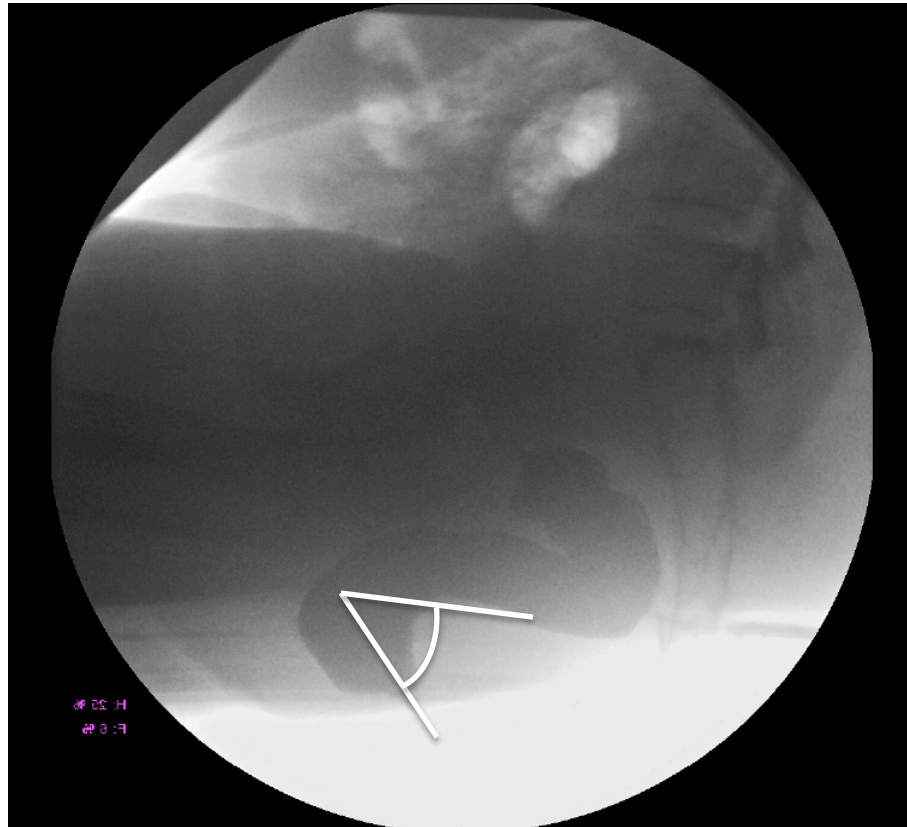


FIGURE 16 – PROCTOGRAPHIC FEATURES OF DYSSYNERGIC DEFACATION: MID DEFAECATION

IMAGE IN THE SAME PATIENT, NOTE THE ONGOING PROMINENT PUBORECTALIS IMPRESSION WITH MAINTENANCE OF AN ACUTE OR HYPERACUTE ANORECTAL ANGLE WITH RESULTANT RETENTION OF NEOSTOOL.

As opposed to anorectal manometry, mechanical or structural causes of rectal evacuatory dysfunction are easily identified by proctography. The most common causes of obstruction are (i) a rectocoele and (ii) an intussusception. A rectocoele is the anterior herniation of the rectum due to a central weakness in the posterior vaginal wall (Abendstein *et al.*, 2008). On proctography it is identified as an anterior bulge outside the line of the rectal wall with resting or straining manouvers (Agachan *et al.*, 1996b) (Figure 19). A rectal wall intussusception, in contrast, results from infolding of the rectal mucosa and/or muscle layer leading to narrowing of the lumen and subsequent obstruction to the passage of proximal stool. Rectal intussusceptae overall are common in both healthy individuals and patients. Non-obstructive intussusceptae (grade 1 – 3, (Figure 17) are usually asymptomatic but more severe, grade 4 and above, intussusceptae can also be found in up to 30 – 50% of healthy subjects (Shorvon *et al.*, 1989, Pomerri *et al.*, 2001). Determining the clinical significance of such a finding can be difficult although, intussusceptae tend to be circumferential and are generally of more advanced morphology in patients compared to asymptomatic controls (Dvorkin *et al.*, 2005a). On proctographic examination, circumferential intussusceptae appear as an annular filling defect (Pomerri *et al.*, 2001). There is poor correlation between presence of intussusceptae and symptoms, and thus the importance of the proctographic finding must be carefully considered (Dvorkin *et al.*, 2005b, Dvorkin *et al.*, 2005a) when making treatment recommendations.

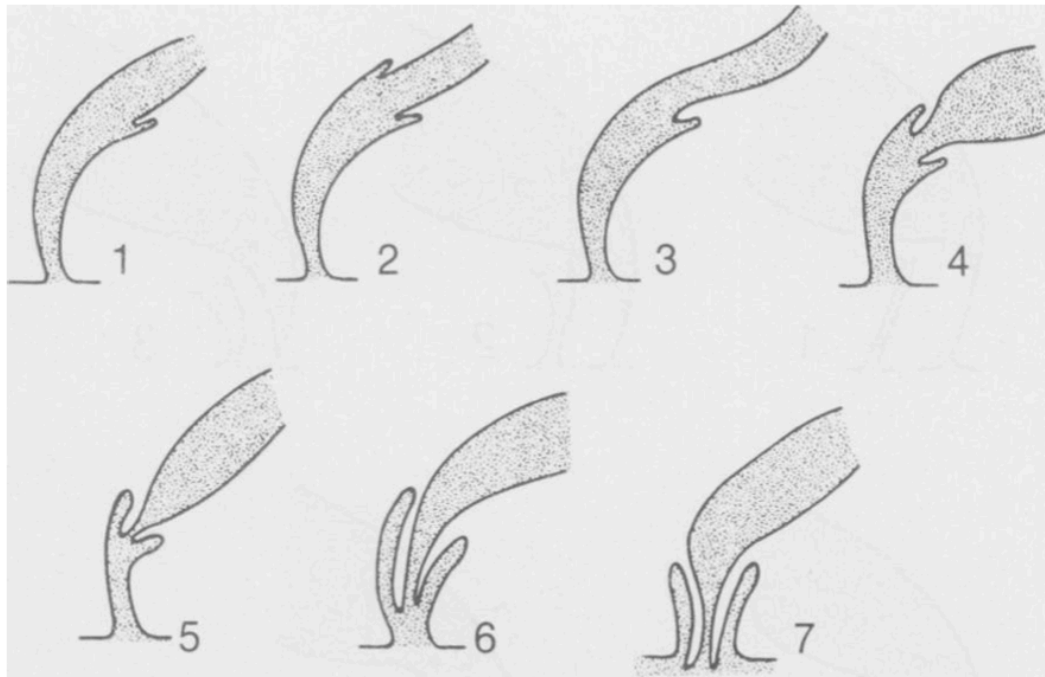


FIGURE 17 – ILLUSTRATIVE GRADING OF INTUSSUSCEPTION AND MUCOSAL PROLAPSE

TAKEN WITH PERMISSION FROM (SHORVON *ET AL.*, 1989): GRADE 1 AND 2 = INFOLDING OF THE RECTAL WALL BY LESS THAN 3MM, PARTIAL AND CIRCUMFERENTIAL RESPECTIVELY, GRADE 3 = NON CIRCUMFERENTIAL INFOLDING OF GREATER THAN 3MM, GRADE 4 = CIRCUMFERENTIAL INFOLDING OF GREATER THAN 3MM WHICH REMAINS INTRARECTAL, GRADE 5 = CIRCUMFERENTIAL INFOLDING OF GREATER THAN 3MM WHICH IMPINGES ON THE INTERNAL ANAL ORIFICE, GRADE 6 = INFOLDING WHICH EXTENDS INTO THE ANAL CANAL AND GRADE 7 = INFOLDING WHICH EXTENDS BEYOND THE ANAL CANAL.

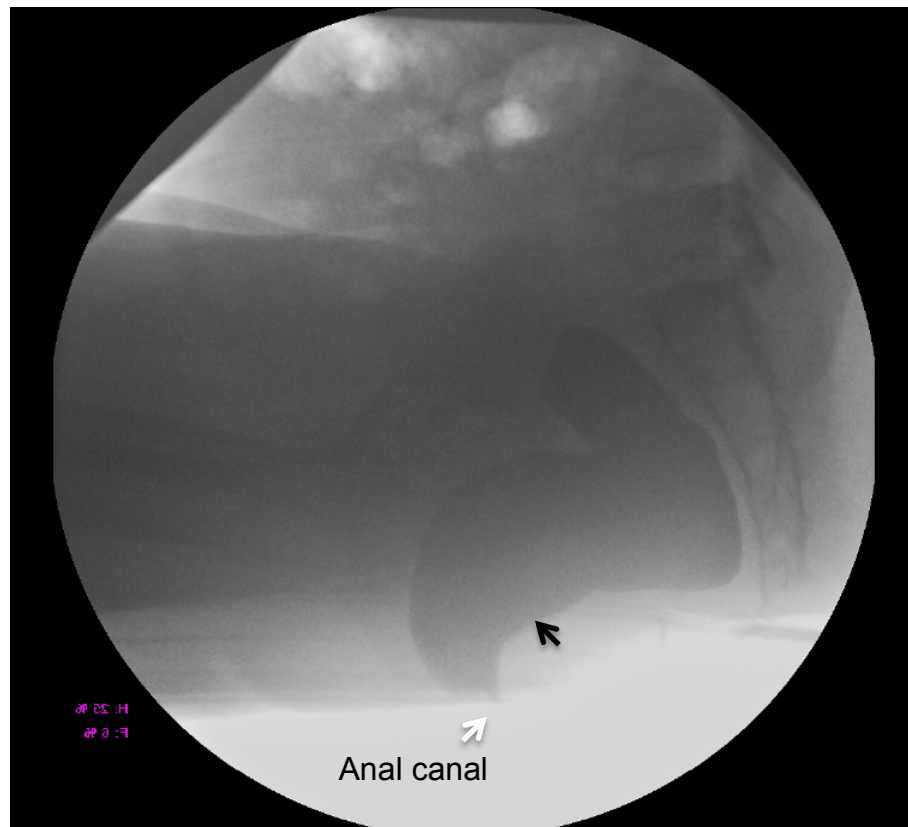


FIGURE 18 — PROCTOGRAPHIC FEATURES OF A RECTOCOELE AND INTUSSUSCEPTION: PRE DEFAECATORY IMAGE

IN THIS IMAGE THE CONTRAST CAN BE SEEN TO FILL THE RECTUM. THE ANAL CANAL IS OUTLINED BY A SMALL LINE OF CONTRAST (WHITE ARROW). NOTE THE INDENTATION OF THE PUBORECTALIS MUSCLE ON THE POSTERIOR WALL OF THE RECTUM (BLACK ARROW).

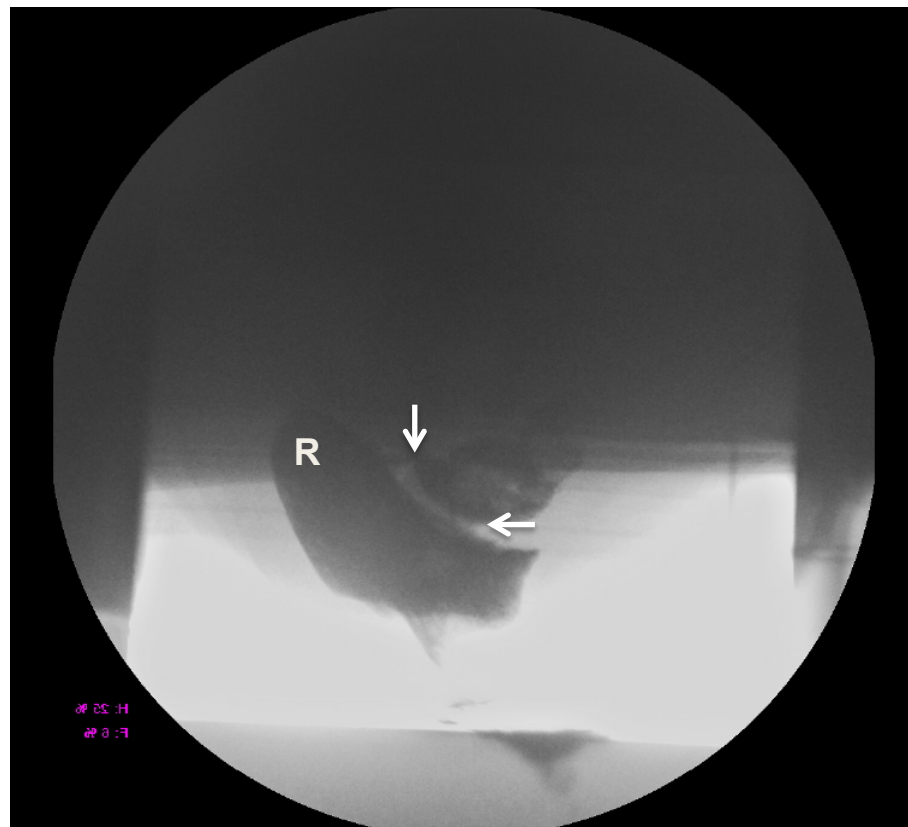


FIGURE 19 — PROCTOGRAPHIC FEATURES OF A RECTOCOELE AND INTUSSUSCEPTION: MID DEFAECATION

IN THE SAME PATIENT, NOTE THE PROMINANT OBSTRUCTIVE INTUSSUSCEPTION / INFOLDING OF THE RECTAL WALL (WHITE ARROW) AND RECTOCOELE (R) PREVENTING EVACUATION OF THE RESIDUAL NEOSTOOL.

Proctography can also be used to determine the presence of a megarectum. Megarectum is a clinically heterogeneous condition and the nomenclature simply refers to the presence of a pathologically dilated rectum on examination under anaesthesia, or traditionally with imaging

studies such as double contrast barium enema or proctography (Gattuso and Kamm, 1997). Patients with megarectum universally have elevated distension volumes to balloon distension (Gattuso and Kamm, 1997), although this only represents afferent dysfunction in a proportion. In the remainder the elevated sensory thresholds to balloon distension are instead secondary to the effects of distending a balloon within an already distended viscus (Figure 10) (Gladman *et al.*, 2009). Given the potential confounding influences of an abnormal rectal diameter on assessments of rectal afferent function, patients were screened for megarectum with proctography (performed on clinical grounds prior to recruitment for further physiological assessment) (Chapter 14 & 15). Megarectum can be diagnosed when the rectum is greater than 8.3 cm at the mid rectal length on proctography at urge threshold (Gladman *et al.*, 2007).

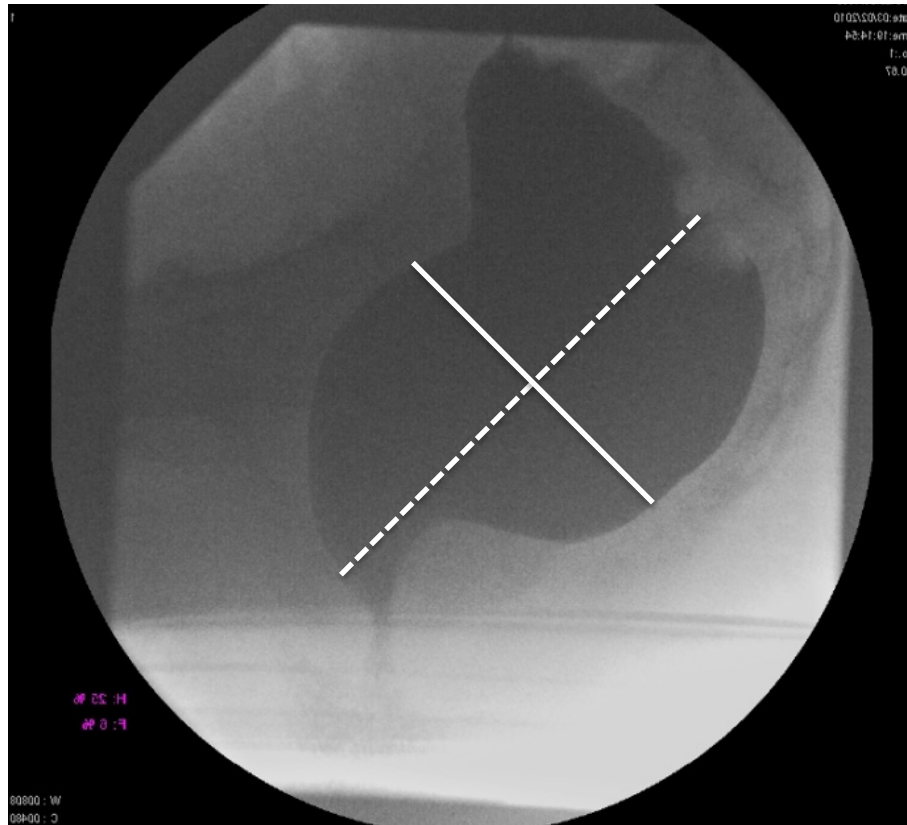


FIGURE 20 - PROCTOGRAPHIC FEATURES OF A MEGARECTUM.

MEGARECTUM DIAGNOSED IF THE RECTAL WIDTH (WHITE SOLID LINE) IS GREATER THAN 8.3CM AT THE MIDRECTAL POINT (DEFINED AS 50% OF RECTAL LENGTH [WHITE BROKEN LINE])

10.3.3.2.1 Limitations

Many centres do not recommend proctography as a first line investigation for constipation or incontinence due to its limited availability, and also its inherent radiation exposure, instead advocating the balloon expulsion test and manometry (as described previously) to diagnose evacuatory dysfunction. However, poor concordance has been found between these tests with regards to diagnostic yield (Palit *et al.*, 2012b). Proctography has the advantage that it records additional structural information to that of either manometry or balloon expulsion. As RH has previously been shown to be primarily associated with functional, as opposed to mechanical obstruction to defaecation, it is critical that the two groups can be distinguished. As a result, proctography has been selected as the investigation of choice for the studies included in this thesis.

10.3.4 Assessment of anorectal structural integrity

10.3.4.1 Endoanal Ultrasound

(Chapters 12, 14 and 15)

Assessment of sphincter structure can be achieved using endoanal ultrasound. Whilst there is evidence to suggest that ultrasound can be used to aid the diagnosis dyssynergia (Brusciano *et al.*, 2007), it is predominantly used clinically to assess whether there is disruption of either the internal or external anal sphincter (Felt-Bersma and Cazemier, 2006) and to assess for perianal disease such as fistulas.

The internal and external anal sphincters are assessed with an endoanal ultrasound probe (10 MHz transducer, B-K Medical, Berkshire, UK) placed within the anal canal. The probe is a mechanical multi-frequency transducer, with two crystals placed back-to-back that rotate within the covering cone to produce a 360° cross-sectional view of the muscle layers (B-K medical transducer 2050 user guide).



FIGURE 21 – THE B-K ENDOANAL TRANSDUCER USED FOR ASSESSMENT OF THE ANAL SPHINCTERS.

THE PROBE IS INSERTED APPROXIMATELY 4 - 5 CM INTO THE ANAL CANAL UNTIL THE TRANSDUCER LIES AT THE LEVEL OF PUBORECTALIS. THE TRANSDUCER IS THEN MOVED DISTALLY DOWN THE CONE TO EXAMINE THE UPPER, MID AND LOWER ANAL CANAL.

The normal layers (Figure 22) of the anal canal seen on endoanal ultrasound (described internal to external) are: (1) the submucosa, which appears as a highly hyperechoic (white) ring adjacent to the ultrasound probe, (2) the smooth muscle internal sphincter (IAS), which appears hypoechoic (black) and is approximately 2 mm thick (up to 3.5 mm in the

elderly), (3) the longitudinal muscle, which is a muscle band external to the IAS with similar echogenicity as the submucosa and, (4) the external sphincter (EAS), which appears as a modestly hyperechoic ring (Rottenberg and Williams, 2002) 4 – 10 mm thick (Felt-Bersma and Cazemier, 2006). The EAS is composed of the deep, superficial and subcutaneous component. In men the EAS is more easily defined and can be seen separate from the longitudinal muscle. The EAS and longitudinal muscle are more difficult to distinguish in women. Beyond the EAS, the anococcygeal ligament, transverse perineal muscles, ischiocavernous muscles, urethra, prostate and pubic bones may be seen (Felt-Bersma and Cazemier, 2006).

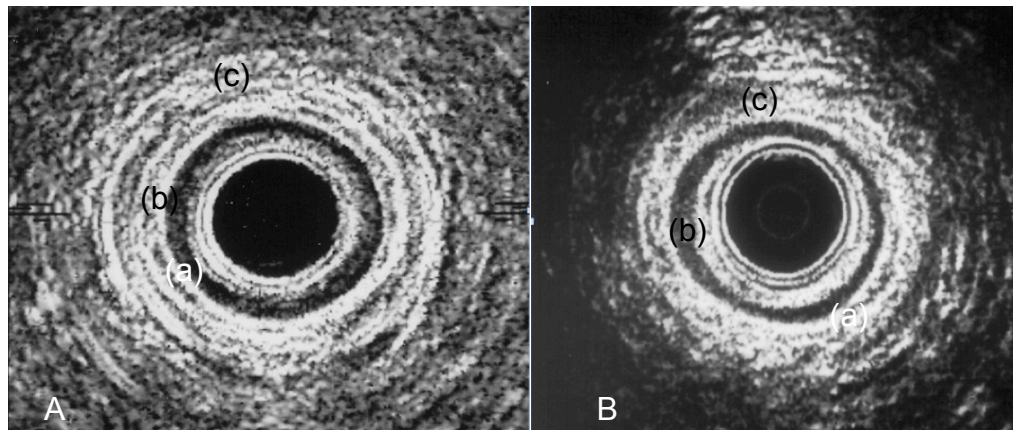


FIGURE 22 – NORMAL APPEARANCE OF THE ANAL SPHINCTERS AT THE MID ANAL CANAL (A) IN MALES AND (B) FEMALES.

THE SPHINCTERS ARE LABELLED (A) INTERNAL SPHINCTER, (B) LONGITUDINAL MUSCLE & (C) EXTERNAL SPHINCTER.

Abnormalities detected on endoanal ultrasound include: (1) disruption of the IAS or EAS or both, seen as a defect (gap) within the sphincter ring (Figure 23), (2) atrophy of the IAS (Figure 24A), (3) atrophy of the EAS, as often seen with sphincter denervation (Beets-Tan *et al.*, 2001), (4) hypertrophy of the IAS, often associated with solitary rectal ulcer syndrome (Figure 24B) and, (5) perianal fistulas or intersphincteric / extrasphincteric collections (Figure 25).

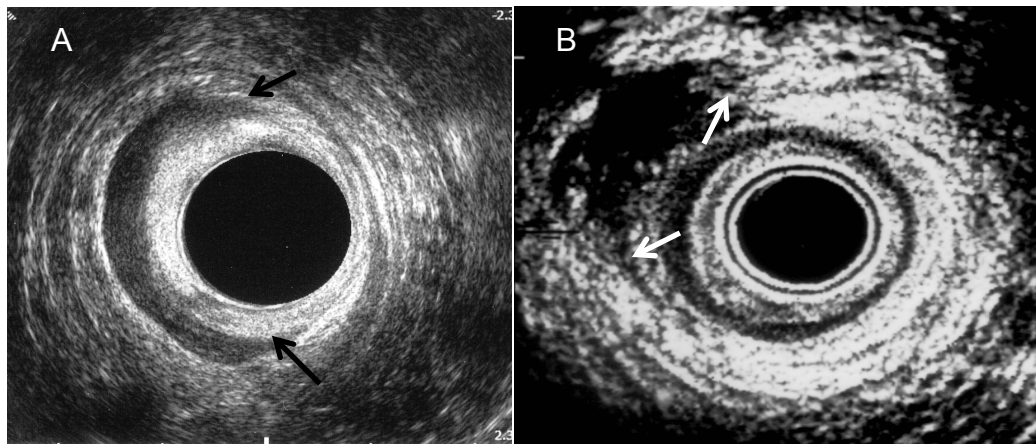


FIGURE 23 – ANAL SPHINCTER DYSRUPTION

(A) INTERNAL ANAL SPHINCTER DISRUPTION BETWEEN 1 AND 5 O'CLOCK (BLACK ARROWS). (B) DISRUPTION OF THE EAS BETWEEN 9 AND 12 O'CLOCK (WHITE ARROWS).

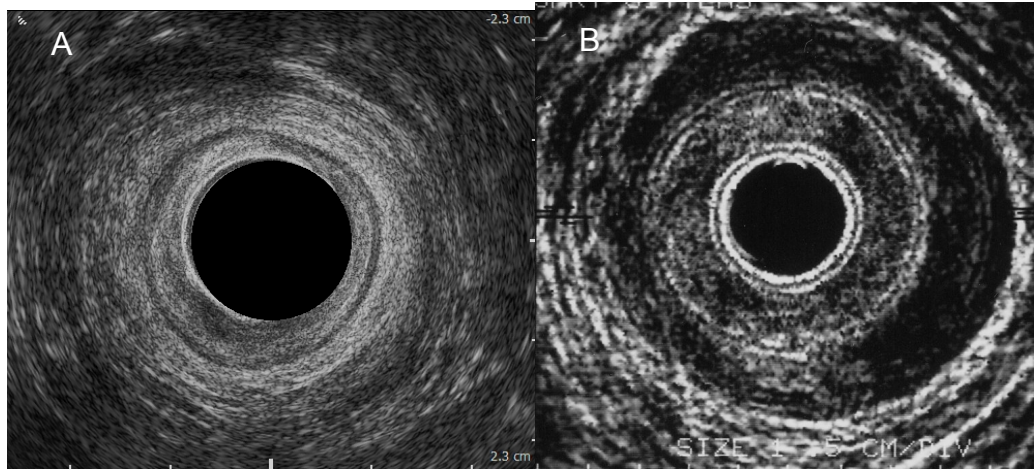


FIGURE 24 – ANAL SPHINCTER HYPERTROPHY AND ATROPHY

(A) INTERNAL SPHINCTER ATROPHY SUGGESTING PRIMARY DEGENERATION OF THE SPHINCTER, (B) HYPERTROPHY OF THE IAS.

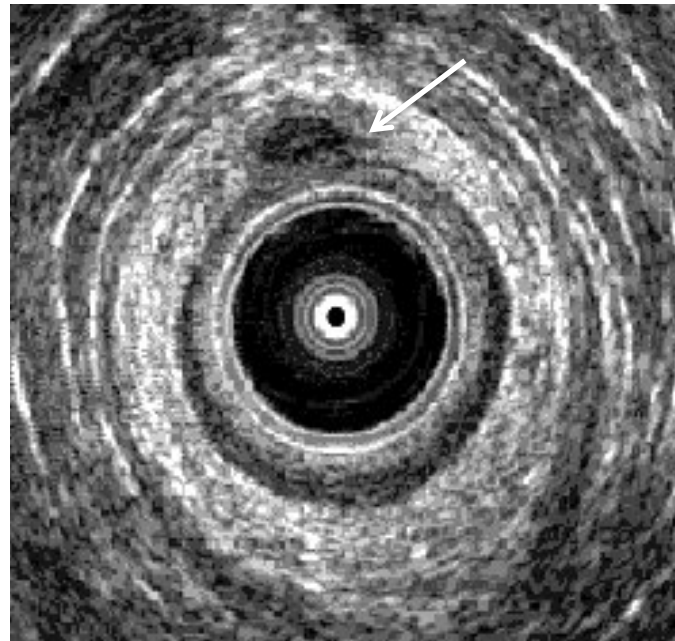


FIGURE 25 – INTERSPHINCTERIC COLLECTION AND FISTULOUS TRACT

(WHITE ARROW).

10.3.4.1.1 Limitations

Whilst ultrasound provides excellent structural resolution it does not provide measurement of sphincter function. Also ultrasound, though reliable when measuring the thickness of the IAS, is less consistent when reporting thickness of the EAS (Beets-Tan *et al.*, 2001).

10.3.5 Assessment of symptoms of bowel function

10.3.5.1 Symptom questionnaires

A number of questionnaires have been developed to assess hindgut symptoms. Some are validated and have been shown to be reproducible. In this thesis the Cleveland Clinic constipation score (CCCS) is utilised to assess symptoms and severity of constipation and the St Mark's incontinence score (SMIS) is used to assess severity of incontinence.

The St Mark's incontinence score was developed in 1999. In comparison to earlier scores (Pescatori score and Wexner score (Pescatori *et al.*, 1992, Jorge and Wexner, 1993), the St Marks score correlates best with clinical assessment and has been shown as the most sensitive instrument to clinical change following intervention (Vaizey *et al.*, 1999a). In comparison to the Wexner score, the St Mark's score has an increased emphasis on the symptom of urgency, with less reliance on whether a pad or constipating medications are required to control symptoms (Table 4).

TABLE 4 – EXAMPLE OF THE ST MARK'S INCONTINENCE SCORE.

THE REPORTED VALUE FROM EACH ROW IS SUMMED TO CREATE THE OVERALL SCORE. REPRODUCED FROM GUT (VAIZEY *ET AL.*, 1999A) COPYRIGHT 1999, WITH PERMISSION FROM BMJ PUBLISHING GROUP LTD.

	<i>Never</i>	<i>Rarely</i>	<i>Sometimes</i>	<i>Weekly</i>	<i>Daily</i>
Incontinence for solid stool	0	1	2	3	4
Incontinence for liquid stool	0	1	2	3	4
Incontinence for gas	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4
				<i>No</i>	<i>Yes</i>
Need to wear a pad or plug				0	2
Taking constipating medicines				0	2
Lack of ability to defer defecation for 15 minutes				0	4
Never, no episodes in the past four weeks; rarely, 1 episode in the past four weeks; sometimes, >1 episode in the past four weeks but <1 a week; weekly, 1 or more episodes a week but <1 a day; daily, 1 or more episodes a day.					
Add one score from each row: minimum score = 0 = perfect continence; maximum score = 24 = totally incontinent.					

The Cleveland Clinic constipation score, developed in 1996, consists of eight variables (Table 5). In validation studies all healthy volunteers returned scores of less than 8. In comparison to clinical review, the score correlates well with severity of constipation (Agachan *et al.*, 1996a). It is also sensitive for detecting response to treatment (Ortiz *et al.*, 2012, Collins *et al.*, 2012), but does not distinguish between physiological subtypes of constipation (Knowles *et al.*, 2000).

TABLE 5 – THE CLEVELAND CLINIC CONSTIPATION SCORE

THE SCORE IS CALCULATED BY ADDING THE SELECTED VALUE OF EACH QUESTION TO GIVE A RESULT BETWEEN 0 AND 30, INDICATING SEVERITY OF SYMPTOMS (AGACHAN *ET AL.*, 1996A).

<h2 style="color: #0056b3; margin: 0;">Cleveland Clinic constipation score</h2> <hr style="border: 0.5px solid #0056b3; margin: 5px auto; width: 50%;"/> <p>Please answer the following questions by circling the answer that best applies to you.</p>	
<p>1. How often do you open your bowels?</p> <p>0 1-2 times per 1-2 days</p> <p>1 2 times per week</p> <p>2 Once per week</p> <p>3 Less than once per week</p> <p>4 Less than once per month</p>	<p>5. How many minutes do you spend in the lavatory when you try to open your bowels?</p> <p>0 Less than 5</p> <p>1 5-10</p> <p>2 10-20</p> <p>3 20-30</p> <p>4 More than 30</p>
<p>2. how often is it painful when you open your bowels?</p> <p>0 Never</p> <p>1 Rarely</p> <p>2 Sometimes</p> <p>3 Usually</p> <p>4 Always</p>	<p>6. Do you need assistance to open your bowels</p> <p>0 No</p> <p>1 Yes - Stimulative laxatives</p> <p>2 Yes – I place my fingers in my bottom or use enemas</p>
<p>3. How often do you feel you have not completely emptied your bowels?</p> <p>0 Never</p> <p>1 Rarely</p> <p>2 Sometimes</p> <p>3 Usually</p> <p>4 Always</p>	<p>7. How many times (per 24 hours) do you try to go to the toilet but are unable to pass anything?</p> <p>0 Never</p> <p>1 1-2</p> <p>2 3-6</p> <p>3 6-9</p> <p>4 More than 9</p>
<p>4. How often do you get abdominal pain?</p> <p>0 Never</p> <p>1 Rarely</p> <p>2 Sometimes</p> <p>3 Usually</p> <p>4 Always</p>	<p>8. How long have you had constipation? (in years)</p> <p>0 0</p> <p>1 1-5</p> <p>2 5-10</p> <p>3 10-20</p> <p>4 More than 20</p>

Data utilised in Chapters 11 and 12 were obtained from an audit of the “Royal London anorectal dysfunction impact score (ADIS)”. This comprehensive questionnaire is routinely employed to aid the clinical assessment of patients within the GI Physiology Unit. It is sent to all patients undergoing anorectal physiological testing along with their appointment letter, and is completed at home, without medical assistance, prior to visiting the hospital. It assesses duration of symptoms, severity, type and frequency of faecal incontinence episodes, as well as pad and / or constipating agent usage and impact on quality of life. Symptoms of constipation are also assessed routinely, including duration of symptoms, laxative use, presence of abdominal pain and bloating, frequency of defaecation, stool form, straining, sense of incomplete evacuation or obstruction, unsuccessful defaecatory efforts, prolonged evacuation, need for digital assistance, and rectal / anal pain. Patients score symptoms by frequency of occurrence, divided into five categories: 0 = never, 1 = rarely (< 25% of the time), 2 = occasionally (25% - 50% of the time), 3 = usually (> 50% of the time) and 4 = always (Mohammed *et al.*, 2010). The questionnaire also allows calculation of previously validated scoring systems: the Cleveland Clinic constipation score (modified) (Agachan *et al.*, 1996a) (score 0 – 30) and the St Mark’s incontinence score (Vaizey *et al.*, 1999a) (score 0 – 24), as described above.

Subjects undergoing advanced physiological assessment (Chapters 14 and 15) completed the standard Cleveland Clinic constipation score and St Mark's incontinence score on the day of the examination.

10.4 Part D: Research techniques used within this thesis

10.4.1 Assessment of bowel sensorimotor function

10.4.1.1 Mechanical barostat

(Chapter 15)

The mechanical barostat has been established as the gold-standard for determining sensation to mechanical distension in the gastrointestinal tract. Assessment of rectal sensorimotor function with the barostat is preferable to latex balloon distension because (1) it is not effected by the inherent recoil properties of the balloon itself; (2) the manner in which the bag is secured at both ends to the catheter limits longitudinal expansion and promotes circumferential distention of the bag / balloon within the viscus and (3) the concurrent recording of pressure and volume allows determination of rectal bioelastic properties (Scott and Gladman, 2008). It is reproducible across laboratories (Cremonini *et al.*, 2005) and between patients (Whitehead and Delvaux, 1997), with known performance characteristics (Cremonini *et al.*, 2005).

A barostat is essentially a computer-controlled piston (Figure 26) connected to an infinitely compliant bag (the volume of which is considerably larger than the viscus in which it is placed, so that the range of volumes used within the study remain below 90% of the maximum volume of the bag (Scott and Gladman, 2008)) mounted on a catheter

(Figure 26), which is inflated and deflated automatically to maintain a constant pressure within the bowel.



FIGURE 26 – BAROSTAT ASSEMBLY

(A) INFINITELY COMPLIANT BALLOON USED FOR RECTAL DISTENSION. (B) COMPUTER CONTROLLED BAROSTAT.

Two methods have been developed for assessing visceral sensation in response to distension: 1) sensory thresholds, and 2) stimulus intensity assessments. A sensory threshold protocol involves gradual distension of the bowel with an infinitely compliant balloon using stepwise increases in pressure with time. This can be done consecutively or based on a pre-set program of varying distension pressures (Scott and Gladman, 2008) via either continuous or phasic distension protocols (Whitehead and Delvaux, 1997). In this protocol the subject is asked to note when the first constant

sensation, urge threshold and maximal tolerable intensity are reached, with hyposensitivity diagnosed as elevated pressure / volumes in comparison to the normal population (Cremonini *et al.*, 2005, Scott and Gladman, 2008). By contrast, the stimulus intensity technique involves distention of the rectum to a program of set pressures, with the subject asked to rate intensity experienced using a visual analog scale (VAS) (Whitehead and Delvaux, 1997, Steens *et al.*, 2002). In this setting, hyposensitivity is diagnosed when the subject reports VAS values below that of the normal range (Scott and Gladman, 2008). Sensory threshold protocols are most commonly utilised, however outcomes can be influenced by psychological factors and thus can be open to response bias. However, if studies are interested in capturing perceptual responses which are dependent on higher cortical function, then such protocols are appropriate (Whitehead and Delvaux, 1997).

The barostat also allows assessment of pressure and volume relationships within the viscus under study, permitting calculation of wall compliance or changes in tone. It is able to stratify patients into those with altered rectal biomechanics, probable isolated afferent defect, or both, in line with prior research which found that although two thirds of patients with RH have altered rectal wall biomechanics, one third have normal compliance suggesting primary afferent dysfunction is responsible for RH. Furthermore, of the individuals with abnormal rectal wall function, approximately one third also have altered mucosal electro-sensitivity

thresholds indicating that afferent nerve function may still be a contributor to the development of RH in such patients (Gladman *et al.*, 2005).

Compliance is the volume response to a change in pressure within the viscus ($C=\Delta V/\Delta P$). The pressure-volume relationship within the rectum is sigmoid in shape and hence compliance is taken as the linear portion of the line of best fit of the pressure- volume plot (Figure 27) constructed from an ascending methods of limits paradigm, as described by the Mayo Clinic group (Cremonini *et al.*, 2005).

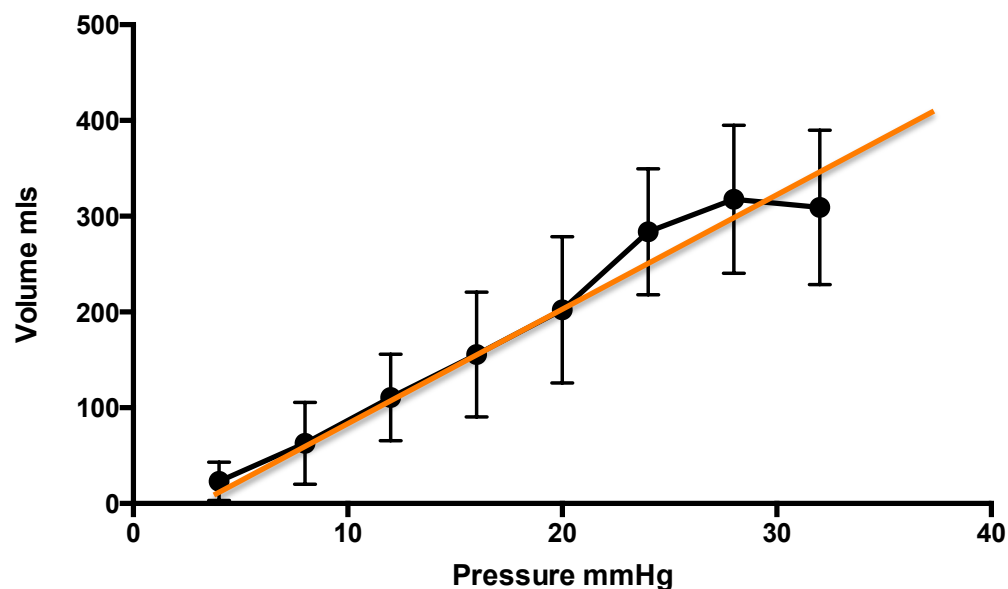


FIGURE 27 – PRESSURE / VOLUME RELATIONSHIP RECORDED VIA ASCENDING METHODS OF LIMIT TESTING DURING BAROSTAT EXAMINATION IN HEALTHY VOLUNTEERS

COMPLIANCE IS CALCULATED AS THE CHANGE IN VOLUME OVER THE CHANGE IN PRESSURE OVER THE LINEAR PORTION OF THE TRACE (RED LINE).

Compliance and sensory threshold recording are influenced by bag length and rate of distension, thus “normal” values must be compared with a data set acquired from control subjects using identical methodology. Thus, as defined in Chapter 15, normal data was derived from healthy volunteers also undertaking the study.

For this thesis an ascending method of limits stepwise distension protocol was used. Stimulus intensity techniques were not appropriate given the large variation in sensory stimulus (pressure) required to induce a response in healthy individuals in comparison to those with RH (i.e. many patients with RH would not be expected to have reached urge threshold at levels beyond that of the maximal tolerable pressures in healthy volunteers). Individualised distension pressures anchored to sensation of first constant sensation; defaecatory desire volume; and maximal tolerable were instead used. As significantly elevated distension volumes were predicted in RH subjects in comparison to healthy controls, it was postulated that the inflation and deflation speed required for phasic distensions would be unequal between groups. As inflation speed has been found to influence sensory perception (Sun *et al.*, 1990c), a continuous, rather than phasic, distension program was employed to minimise potential for confounding.

10.4.1.1.1 Limitations

The use of “compliance” as a measure of distensibility or wall stiffness, as determined by Barostat distension, has been criticised. Compliance fails to take into account the wall thickness, variations in the unstressed luminal dimensions or actual degree of wall stretch under pressure loading (Gregersen and Kassab, 1996). Also, rectal wall mechanoreceptors are not pressure receptors *per se*, more likely responding to circumferential rectal wall stretch or strain (Gregersen and Kassab, 1996). As a result, techniques have been developed which provide measures of rectal cross-sectional area using an impedance planimetry probe (Brock *et al.*, 2008). Whilst impedance planimetry provides better measures of wall tension, stretch and strain, as it calculates radial distension more accurately than volume based techniques (i.e. barostat) (Brock *et al.*, 2009), impedance requires distension of the stimulating balloon with 0.009% saline (to a maximal volume of 240ml (Brock *et al.*, 2008)). Given that it was predicted that larger volumes would be required to elicit sensation in patients with RH, this technique was not thought suitable, as the excess weight of the fluid in the pelvis was considered to be a significant confounder. As a result, despite the discussed limitations associated with the use of compliance as a measure of rectal wall viscoelasticity, it was felt to be the most robust measurement in the current patient group.

10.4.2 Assessment of visceral afferent nerve function

10.4.2.1 Rectal electrical sensory thresholds

(Chapter 14 and 15)

Testing is performed via stimulation with a bipolar electrode mounted 1 cm apart, 2 cm from the tip of a flexible catheter (Gaeltex Devices, Isle of Skye, Scotland).

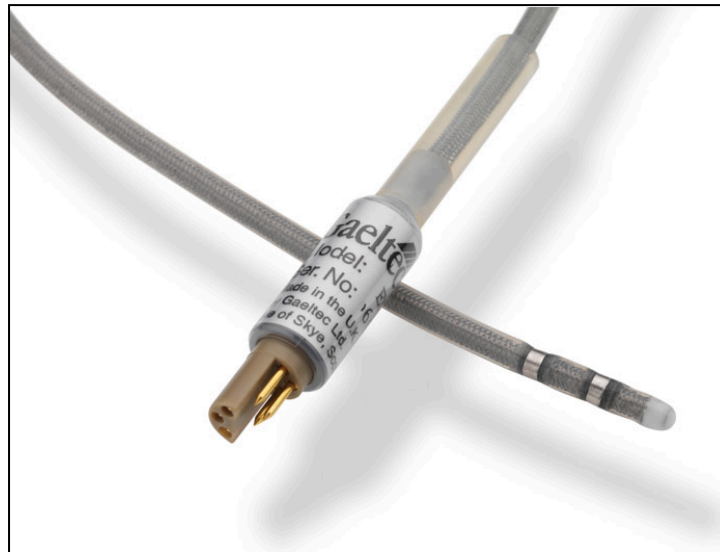


FIGURE 28 – GAELTEC BIPOLAR ELECTRODE STIMULATING CATHETER USED FOR ELECTRICAL STIMULATION OF THE RECTAL MUCOSA

The catheter is inserted through the anal canal, with the stimulating electrode placed 10 cm from the anal verge. The rectal mucosa was stimulated with a square pulse of 0.2 ms duration (Hobday *et al.*, 2000), at a frequency of 0.2 Hz (Hobday *et al.*, 2002). Three sensory thresholds were determined: (1) first sensation, the intensity at which sensation is first felt within the pelvis; (2) pain threshold, the intensity at which the stimulus

is first felt as painful; and (3), maximal tolerable sensation, the intensity at which the subject requested the stimulation to stop.

10.4.2.1.1 Limitations

While luminal distension is more physiological than electrical stimulation, the advantage of mucosal electrosensitivity testing is its independence of wall biomechanics theoretically; therefore providing a more robust assessment of afferent nerve function (Scott and Gladman, 2008). However the exact sensory pathways being activated are not clear (Meagher *et al.*, 1996). Rectal wall electrical stimulation bypasses rectal receptors, activating nerve fibres directly (Hobday *et al.*, 2000). Whilst it is likely that afferent fibres within the rectal wall are being activated, nerve fibres in the pelvic floor may also be stimulated (Loening-Baucke *et al.*, 1992, Meagher *et al.*, 1996). In addition, response to electrical stimulation is dependent on good rectal wall contact, something that is often difficult to achieve given varying anatomy between patients. Early studies have suggested that poor wall contact significantly affects sensory thresholds (Meagher *et al.*, 1996). While it was possible to ensure contact with the rectal wall (by performing rectal examination at the time of insertion of the catheter), it was not possible to guarantee that this was unchanged throughout the study. Therefore, to confirm wall apposition, for the studies (Chapter 14 and 15) within this thesis, impedance across the stimulating electrodes was recorded and, if it was elevated ($>3k\Omega$), a latex balloon

was inserted alongside the probe and inflated to just below sensory threshold to ensure mucosal apposition.

The normal range of threshold values for mucosal electrical stimulation is dependent on the duration and frequency of stimulation parameters. For example, longer pulse duration effectively produces an increased stimulation intensity with resultant lowered sensory threshold values. Therefore patient values should be assessed against healthy controls examined with an identical protocol. For each study within this thesis (Chapter 14 and 15), normal values were determined by healthy controls within the study.

10.4.2.2 Cortical evoked potentials

(Chapter 14 and 15)

With the advent of neuromodulation as a recognised effective treatment for hindgut dysfunction, there has been renewed interest in the study of the neuronal pathways responsible for the function of the rectum. Evoked potentials (EP) are attractive as they allow interrogation of the neurophysiological pathways of the gastrointestinal afferent nervous system, via an electroencephalograph (EEG), to non-invasively measure the direct brain activity in response to a painful stimulus delivered within the organ of interest. Each evoked potential maps the transmission of sensory information throughout the afferent neuronal pathway to the cortical areas. Each stimulus is recorded at a discrete point in time

allowing the neuronal electrical response to the stimulus to be extracted from the background brain activity.

Somatosensory evoked potentials are a widely used neurophysiological tool to investigate afferent neuronal function (Hobday *et al.*, 2002, Lefaucheur and Creange, 2004), however, the use of visceral evoked potentials (such as rectal evoked potentials: REP's) in clinical research is still evolving. Nevertheless, this technique has been employed extensively in healthy volunteer studies (Loening-Baucke *et al.*, 1992, Hobday *et al.*, 2002, Harris *et al.*, 2006, Garvin *et al.*, 2010, Remes-Troche *et al.*, 2011), and used to demonstrate changes in afferent neuronal function in patients with visceral hypersensitivity and irritable bowel syndrome (Sinhamahapatra *et al.*, 2001, Rossel *et al.*, 2001) as well as childhood chronic constipation (Loening-Baucke and Yamada, 1995, Kubota *et al.*, 1997).

10.4.2.2.1 Limitations

Painful electrical stimulation of the rectum is non-physiological in nature, as the receptor is bypassed with the nerve itself directly stimulated (Hobday *et al.*, 2000). Rectal EP's can be induced in a more physiological manner by using rapid balloon distension, however EP's produced using this technique have been shown to be less robust (Hobday *et al.*, 2000). In addition, given the study cohort where many of the patients were expected to have increased rectal dimensions or altered rectal biomechanics,

balloon distension was not considered ideal, as the time required for adequate balloon insufflation and deflation may be increased in some subjects (as a larger volume would be required to elicit sensation). This would have the potential to alter the parameters of the stimulation in the hyposensitive group and thus, the stimulation would not be equal between each groups. Electrical stimulation was hence preferred in the studies included in this thesis as it is more reliably quantified and its rapid time course produces superior EP's to that of balloon distension (Hobday *et al.*, 2000).

There is debate as to the optimal stimulating parameters for inducing rectal evoked potentials. This particularly applies to intensity of stimulation. This has been evaluated by a number of studies. Stimulation intensity is generally delivered in an individualised manner based on subjective sensation thresholds. A standardised stimulus is not suitable for visceral studies due to the large range within which normal electrical stimulation thresholds are experienced. However, it is acknowledged that this approach relies on the assumption that two individuals experience the same quality of sensation (although at different stimulation intensities), and does not take into account the influence of higher cortical centres on pain processing. The optimal intensity for stimulation is generally described as 75% between sensation thresholds and maximal tolerable sensation (MTS) (Hobson *et al.*, 1998, Harris *et al.*, 2006). However, in the studies included in this thesis, pain threshold was chosen, as opposed to

MTS, as it was hypothesised that a sizable proportion of hyposensitivity patients would be unlikely to reach MTS within the preset safety limit.

10.4.2.3 Inverse modeling

(Chapter 14)

In addition to yielding information regarding conduction velocity and response amplitude, spatial localization of brain generators (dipole sources) can be extrapolated from evoked potential data via analysis using “inverse modelling” (Drewes *et al.*, 2004, Sharma *et al.*, 2009). The “inverse problem” aims at reconstructing the original current distribution in the human brain using potential differences measured non-invasively from the scalp via an electroencephalogram (EEG). This allows estimation of pathways taken by the neuronal impulse as it moves through higher cerebral centres. This form of mathematical modelling has been validated in healthy volunteers (Drewes *et al.*, 2004), patients with irritable bowel syndrome (Drewes *et al.*, 2005), and patients with chronic abdominal pain (Olesen *et al.*, 2010), but has yet to be employed in constipated patients.

Dipole sources are formed by: the location of current flow in the cortex; orientation (determined by the direction of current flow, which in turn is a result of the orientation of pyramidal cells within the grey matter, i.e. currents at cortical convexity have a radial orientation whereas currents in a cortical fissure will have a tangential orientation); amplitude (the product of post-synaptic current flow measured in dipole moments); and length,

over which the current is transmitted. When combined with temporal information in all channels (giving specific weights to each signal), source waveforms are calculated.

Electroencephalogram electrodes, used for recording evoked potential data, record voltage (i.e. electrical potential difference between the electrode of interest and a reference electrode) over the scalp. This electrical difference is produced as current flows within the grey matter of the cortex. This can be converted using brain electrical source analysis (BESA) software (BESA Research 5.3, MEGIS Software GmbH, Gräfelfing, Germany) into a topographic map showing scalp potentials derived from all electrodes simultaneously. Many different source configurations may explain the scalp potentials recorded. Scalp data is also influenced by “noise” from within the cortex and external influences. It is important to note that inverse-modeling does not determine the “correct” or “true” dipole source but, by applying known *a priori* constraints to the model (i.e. effect of head properties, number of dipoles, anatomical appropriateness), aims to determine the “best fit” of dipole source models with the experimental data (Figure 29).

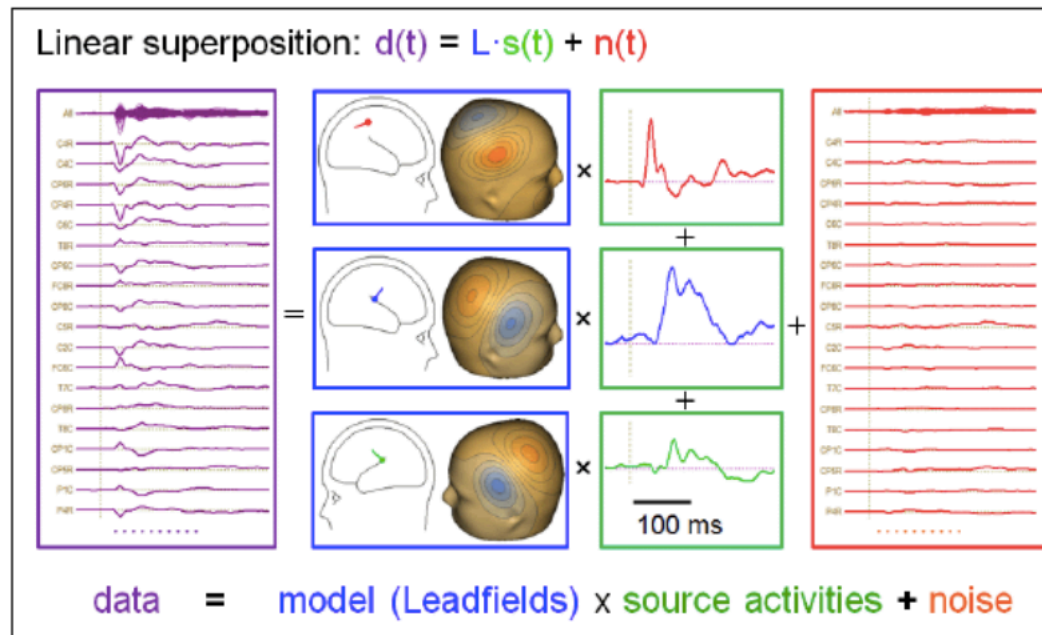


FIGURE 29 – DETERMINATION OF THE INVERSE SOLUTION

THE INVERSE SOLUTION IS DEPENDENT ON THE HEAD MODEL UTILIZED, EEG “NOISE” AND SOURCE ACTIVITY. WITH PERMISSION WWW.BESA.DE

The “best fit” model is determined by comparing the model waveform with the data waveform and determining the “residual variance”; the proportion of the data waveform that is not explained by the model (Figure 29). A residual variance of less than 10% is considered a good fit (Maurits, 2011).

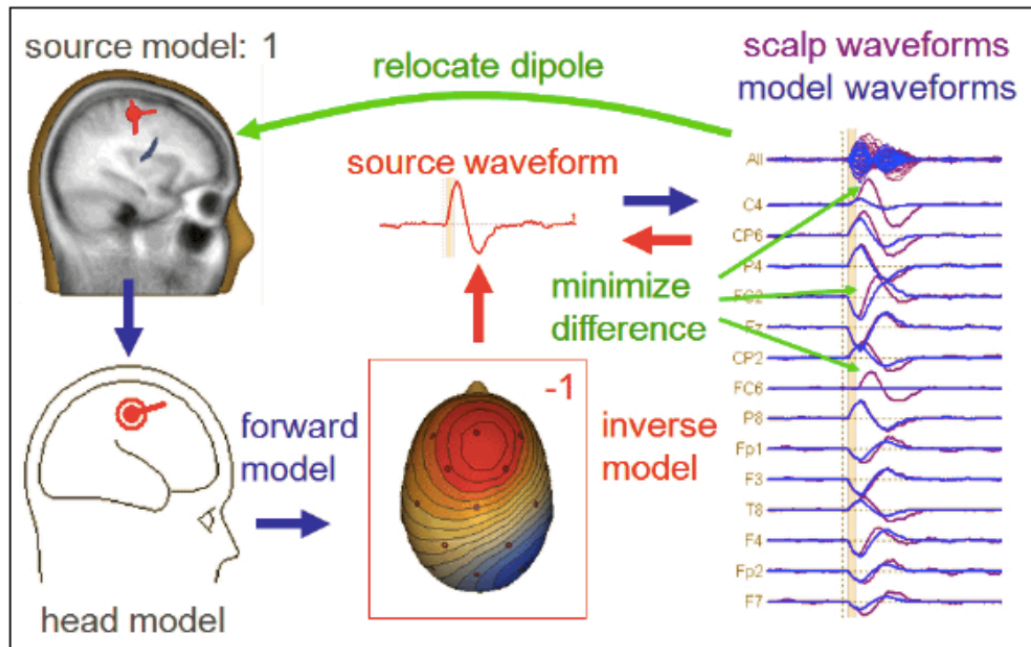


FIGURE 30 – DETERMINING "BEST FIT" USING INVERSE MODELLING

BY USING THE HEAD MODEL, THE FORWARD MODEL TOPOGRAPHY IS ESTIMATED. THIS MODEL IS THEN USED TO DETERMINE THE DIPOLE SOURCE WAVEFORM WHICH IS THEN CONVERTED TO A MODEL SCALP WAVEFORM AND COMPARED WITH THE ACTUAL SCALP WAVEFORM. DATA NOT EXPLAINED BY THE MODEL IS CALLED RESIDUAL VARIANCE. DIPOLE LOCATION AND ORIENTATION IS THEN CONTINUOUSLY ADJUSTED TO ACHIEVE THE LOWEST RESIDUAL VARIANCE OR BEST FIT. WITH PERMISSION WWW.BESA.DE

10.4.2.3.1 Limitations

Inverse modeling is highly dependent on the placement and number of recording electrodes, the choice of reference electrode, as well as the interpolation techniques employed (Michel *et al.*, 2004). In these studies, EP's were recorded using 64 electrode channels referenced against linked ear references. The choice of inverse model utilised is also critical. In this thesis, spline interpolation and the LORETA (Laplacian weighted Minimum Norm) model were used (Michel *et al.*, 2004). LORETA was utilised, as it

has no *a priori* constraints as to the number of dipoles used within the model, however produces smoothed spatial distributions which can produce over “blurred” solutions (Michel *et al.*, 2004).

10.4.3 Assessment of visceral efferent nerve function

10.4.3.1 Transcranial and translumbar magnetic stimulation

(Chapter 15)

First described in 1985 by Barker *et al* (Barker *et al.*, 1985), transcranial and translumbar magnetic stimulation can be used to examine central and peripheral efferent neuronal pathways (Rossini and Rossi, 2007). Unlike electrical stimulation, the technique is non-invasive and essentially painless.

In essence, the magnetic stimulator produces a pulse of electromagnetic current of sufficient strength to depolarise neurons, that is then focused to the region of the cortex corresponding to the motor area of interest (Groppa *et al.*, 2012). Alternatively, the sacral or spinal nerve roots can be stimulated directly by positioning the coil (Figure 31) over the spine or sacrum. The coil is then discharged, causing either excitation or inhibition of the neuron, depending on the protocol, and the propagation of an action potential leading to the activation of muscle fibres (Kobayashi and Pascual-Leone, 2003).



FIGURE 31 – EQUIPMENT UTILISED DURING MAGNETIC STIMULATION OF LUMBOSACRAL NERVE ROOT AND CORTEX

A) 70MM DIAMETER STIMULATING COIL FOR LUMBOSACRAL STIMULATION, B) THE MAGSTIM 200 AND C) STIMULATING 110MM DOUBLE CONE COIL FOR CORTICAL STIMULATION (MAGSTIM CO. LTD, CARMARTHENSHIRE, UK).

Transcranial magnetic stimulation (TMS) can be used to study the central motor conduction times by recording the latencies between stimulation and the onset of the recorded motor evoked potential (MEP). By delivering stimulation to different levels of the motor pathway (cortex, corticospinal tract, peripheral motor nerves), localisation of pathology can be determined by comparing the conduction time from proximal to distal (Weber and Eisen, 2002, Rossini and Rossi, 2007). In addition, TMS can help to distinguish between axonal or demyelinating conditions. Prolongation of the conduction time suggests demyelination, whereas

decreased amplitude responses with normal latencies indicates axonal injury (Hallett, 2000).

10.4.3.1.1 Limitations

Technical factors

TMS is a non-selective stimulation technique, resulting in the stimulation of multiple neuronal elements in the area surrounding the impulse. Therefore, selectivity is instead achieved by localisation of the recording device to the muscle group of interest. In the pelvic floor, this can be particularly troublesome. Previous studies have been able to comfortably record MEPs from the anal sphincter (Herdmann *et al.*, 1991, Harris *et al.*, 2006), the puborectalis muscle (Brostrom, 2003, Brostrom *et al.*, 2003a, Brostrom *et al.*, 2003b), and recently, the rectal wall (Tantiphlachiva *et al.*, 2011, Remes-Troche *et al.*, 2011).

Coil choice is also a critical part of study design. To penetrate deeply (i.e. to stimulate the motor area responsible for the pelvic floor) a large round coil should be selected. Unfortunately, this also results in a less targeted stimulation. In addition, magnetic stimulation preferentially activates neurons orientated horizontally, requiring precise positioning of the stimulating coil to ensure reproducibility (Kobayashi and Pascual-Leone, 2003).

Patient factors

The MEP recorded is influenced by the activity of the muscle of interest. Activation of the muscle can be used to facilitate the MEP response and this must be accounted for when educating the subject. Sustained contraction can result in a shortened latency, increased amplitude and reduction in the intensity required to elicit a motor response. However, once the muscle is activated beyond 20% of the maximum voluntary contraction, further contraction does not result in significant latency change (Weber and Eisen, 2002). Nevertheless, the goals of this study were to analyse the motor potential latency, and therefore, it was not essential to quantify the absolute force of the target muscle contraction.

11 CLINICAL IMPACT OF RECTAL HYPOSENSITIVITY ON SYMPTOMS OF HINDGUT DYSFUNCTION.

11.1 Introduction

Impaired or blunted rectal sensation, termed rectal hyposensitivity (RH), is associated with disorders of hindgut function. However, the true clinical impact of the physiological finding of RH has not been clearly defined. Previously, Harraf *et al.* (Harraf *et al.*, 1998) found that RH appeared to be associated with “no urge constipation” and Gladman *et al.* (Gladman *et al.*, 2003a), found RH commonly in constipated patients, patients with faecal incontinence, and patients with symptoms of both. Furthermore, RH was most often seen in constipated patients with “functional” rather than a mechanical (anatomical) obstruction to defaecation (Gladman *et al.*, 2003a). However, neither study addressed in detail patient’s presenting symptoms or severity of illness using recognised scoring systems.

Whilst rectal sensation is clearly integral to hindgut function, and indeed normalisation of aberrant rectal sensation in constipation is associated with symptomatic improvement (Rao *et al.*, 1997, Lee *et al.*, 2006, Knowles *et al.*, 2012), a clear clinical phenotype associated with RH has not been established.

This study is aimed to determine whether, in a large cohort of patients with hindgut dysfunction, RH is associated with a specific clinical phenotype and / or influences the severity of patient presentation.

11.2 Methods

A retrospective review of prospectively collected data was undertaken. All patients presenting for investigation of hindgut dysfunction over a ten-year period (2003 – 2012), who had the results of comprehensive gastrointestinal physiological investigations available, and who had completed a comprehensive symptom questionnaire (see Chapter 10) were considered eligible (n = 5204). Questionnaires were considered “complete” if at least 85% of questions were answered. If up to two questions were missing within the dataset, statistical imputation was used to complete the data. The ‘Impute’ function fills in incomplete values, considering these to be dependent variables in missing-value regressions. The imputation regression is based upon statistical patterns across the entire data set using dependent variables calculated from all other answers to questions provided by the patients (independent variables) to create a new variable containing the imputed values. Patients diagnosed with rectal hyposensitivity (as previously defined) were selected (cases), and were compared with randomly selected patients matched by age, sex and parity but with normal rectal sensation (controls).

11.2.1 Clinical information

In all patients, data collected included patient demographics (age, sex, year of review), predominant symptoms, as well as a completed comprehensive symptom questionnaire used routinely within the Unit (Mohammed *et al.*, 2010). This allowed the calculation of the Cleveland Clinic constipation score (CCCS) and St Mark's incontinence score (SMIS), as well as determining the frequency of key symptoms as defined by the ROME III criteria (Longstreth *et al.*, 2006, Bharucha *et al.*, 2006) for the diagnosis of constipation and incontinence. Patients were also asked two questions pertaining to health status and impact of symptoms on quality of life. Patients were asked to rate their current health as "very poor", "poor", "fair", "good" or "very good". In regards to impact of symptoms on lifestyle, patients selected that "symptoms impacted on their daily lives": "a lot", "quite a bit", "moderately", "a little bit" or "not at all".

11.2.2 Investigations

All patients underwent comprehensive anorectal physiological testing with the rectum unprepared (Chan *et al.*, 2005a) as described in Chapter 10. Several practitioners undertook these investigations, all adhering to a standardised method. All patients underwent assessment of rectal sensation.

11.2.3 Statistical analysis

Demographics, symptom scores, symptom duration, symptom frequency and measures of quality of life and health status were compared between patients with RH or without (normal sensation: NS). For between groups analyses (i.e. symptom scores), a t-test or Mann-Whitney U test, depending upon Gaussian distribution, were utilised where appropriate. Categorical statistical analysis was performed by a Fisher's exact test or Chi square test. A *P* value of <0.05 was considered statistically significant. Analyses were performed using a commercially available statistical software package (Prism 5.0 GraphPad Software, San Diego, CA, USA).

11.3 Results

Eight hundred and forty eight patients with a clinical diagnosis of rectal hyposensitivity were identified over the study period (equating to 16% of the total study population). Of these, 702 patients had adequately completed the symptom questionnaire and undergone physiological investigations including rectal sensory threshold testing and thus were considered eligible for the study. Thirty-four patients were unable to be matched due to extremes of age (i.e. <16 years old, > 95 years old) and parity (i.e. > 9 children) leaving 668 patients to be matched. Controls (*n* = 668) were randomly selected from the same population (known to have normal rectal sensation). This provided a total of 1336 patients for analysis.

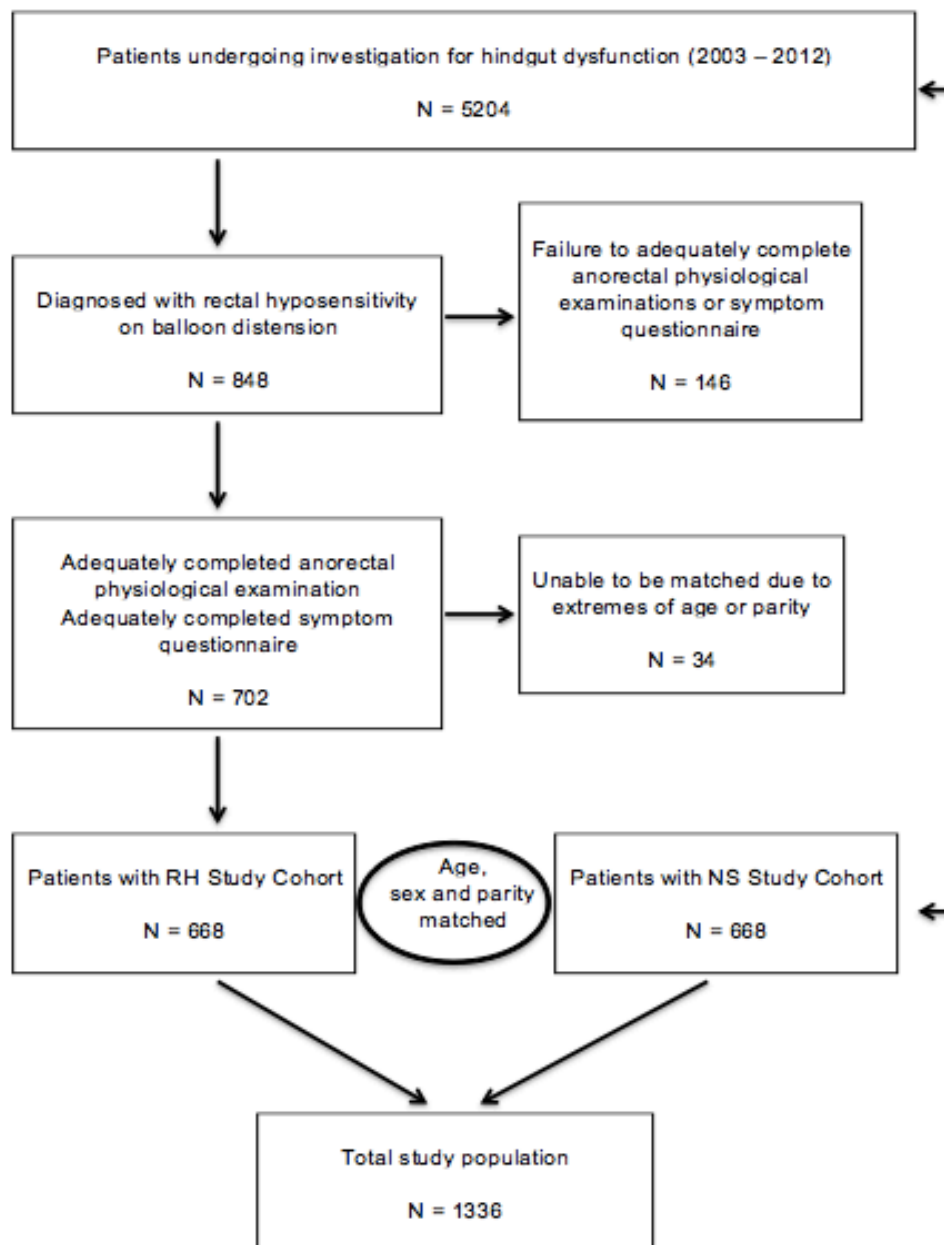


FIGURE 32 – OVERVIEW OF PATIENT DISPOSITION WITHIN THE STUDY

Overall mean age was 51.6 years and the majority (76%) were female. Of the parous females (n = 848), 128 women had one child, 380 women had two children, 214 women had three children and 126 women had four children or more. 198 women were nulliparous. Of the patients with RH, 239 (36%) had one elevated sensory threshold, 256 (38%) had two elevated thresholds and 173 (26%) had three elevated levels.

TABLE 6 – SUMMARY OF DEMOGRAPHICS NORMAL SENSATION AND RECTAL HYPOSENSITIVITY

EXPRESSED AS NUMBER (% OF WHOLE DATA SET). PATIENTS MATCHED BY AGE, SEX AND PARITY.

	Normal sensation	Rectal hyposensation
Men	145 (24%)	145 (24%)
Women	523 (76%)	523 (76%)
Age (mean (range))	51.6 (16 – 85)	51.6 (16 – 85)
Nulliparous women	99 (14%)	99 (14%)
One child	64 (9%)	64 (9%)
Two children	190 (28%)	190 (28%)
Three children	107 (16%)	107 (16%)
Four or more children	63 (9%)	63 (9%)

11.3.1 Presenting symptoms

Almost one-third of patients overall described constipation alone, 21% incontinence alone and 43% of patients described both constipation and incontinence. Twenty-three percent of patients had been previously labeled as suffering from irritable bowel syndrome on information volunteered by the patient. The median CCCS was 13 (IQR 8 – 18) and median SMIS incontinence score was 8 (IQR 4 – 13). Patients with RH were more likely to describe constipation (NS = 69% vs. RH = 77%, OR 1.5 (1.3 – 2.0); $P < 0.0006$) and, while there was no difference in rates of incontinence overall, patients with RH were less likely to report isolated incontinence in the absence of constipation (NS = 25% vs. RH = 17%, $P = 0.0007$). Patients with RH were less likely to have a prior “diagnosis” of irritable bowel syndrome (OR 0.7 (95% CI 0.5 – 0.9); $P=0.009$).

Sensory status also significantly influenced the severity of constipation as measured with the CCCS. Patients with RH reported a higher score (median NS = 12 vs. RH = 15; $P < 0.0001$) (Figure 33) and were twice as likely to score greater than 20 (NS = 10% vs. RH = 20%, OR 2.1 (95%CI 1.5 – 2.8); $P < 0.0001$), consistent with severe constipation.

Sensory status did not influence severity of faecal incontinence as measured by the SMIS incontinence score (NS = 8 (IQR 4 – 13) vs. RH = 8 (IQR 4 – 13); $P = 0.5$) (Figure 33).

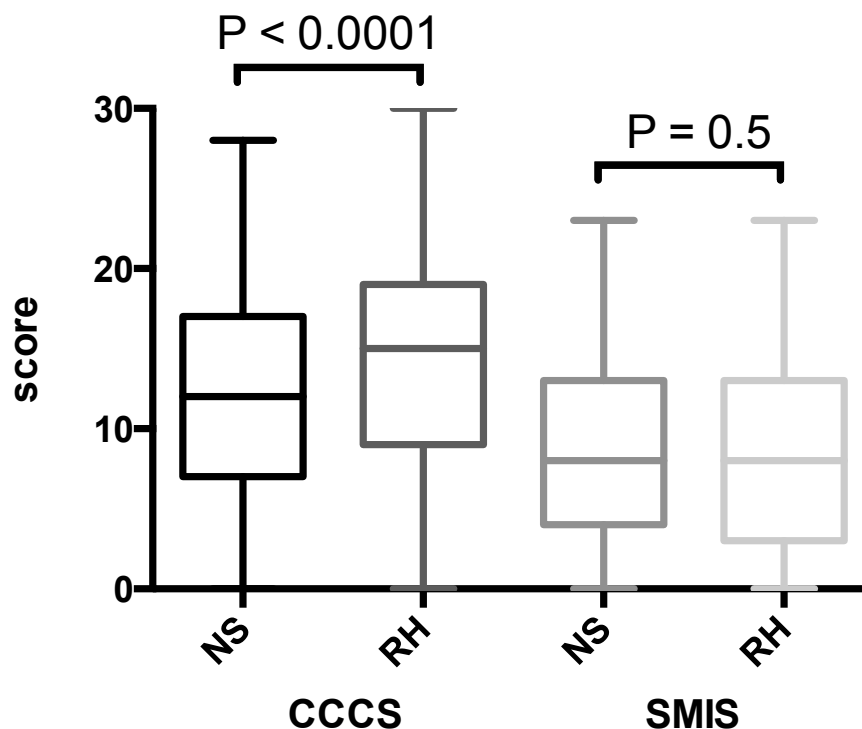


FIGURE 33 – COMPARISON OF SYMPTOM SEVERITY BY SENSORY STATUS UTILISING THE CLEVELAND CLINIC CONSTIPATION SCORE (0 – 30) AND THE ST MARK'S INCONTINENCE SCORE (0 – 24). MEDIAN (IQR), MIN, MAX.

11.3.2 Patterns of defaecation

(Table 7, Table 8)

Overall 70% of patients noted normal defaecation frequency (at least every second day). This was more likely in patients with normal sensation (NS = 78% vs. RH = 62%; $P < 0.0001$). However, infrequency of defaecation was by contrast significantly associated with the presence of RH (Table 7). Furthermore the lower the defaecation frequency the higher the odds ratio that patients had RH (e.g. bowels open two times a week, odds ratio RH : NS 1.5 (1.1 – 2.0); bowels open less than fortnightly, odds ratio = 2.5 (1.3 – 4.6)).

TABLE 7 – FREQUENCY OF DEFAECATION IN PATIENTS, CASES (RH) AND CONTROLS (NS)

Frequency of defaecation	Odds ratio RH/NS	p-value
Bowels open at least every 1 – 2 days	0.44 (0.35 – 0.56)	<0.0001
Bowels open 2 x a week	1.5 (1.1 – 2.0)	0.02
Bowels open weekly	1.8 (1.1 – 2.8)	0.02
Bowels open less than once per week	2.4 (1.4 – 4.0)	0.0009
Bowels open less than once a fortnight	2.5 (1.4 – 4.6)	0.004

While the majority of patients (37%) described a normal toileting time (less than 5 minutes), 22% described a toileting time of 5 – 9 minutes, 17% reported taking 10 – 19 minutes, 7% reported taking 20 – 29 minutes, and 15% took over 30 minutes to evacuate their bowels. However, there was no difference in toileting time found between sensory groups.

Over 50% of patients described hard stools more than 25% of the time. This was more common in patients with RH (NS = 51% vs. RH = 59%; $P = 0.005$).

When comparing specific symptoms of rectal evacuatory dysfunction, 55% of patients were unable to evacuate despite an urge to do so more than 25% of the time. This was more likely in patients with RH, OR 1.5 (1.2 – 1.9); $P = 0.003$. The majority of patients (82%) reported a sense of incomplete emptying more than 25% of the time, and again this was more likely in patients with RH, OR 1.6 (1.2 – 2.1); $P = 0.001$. Patients also commonly (57%) noted anal pain with defaecation more than 25% of the time and 61% of patients described abdominal pain more than 25% of the time. Both presence of anal pain (OR 1.3 [1.1 – 1.6], $P=0.009$) and abdominal pain (OR 1.3 [1.02 – 1.6]; $P = 0.03$) was more commonly found in patients with RH.

Almost 50% of the study population required either enemas or digitation to aid rectal emptying and 17% used stimulant laxatives. Patients with RH were more likely to require enemas or manual manoeuvres to facilitate defaecation (RH = 54% vs. NS = 43%, OR 1.6 [1.3 – 1.9]; $P<0.0001$).

The results remained generally consistent when a conservative Bonferroni correction was applied to the data (which determined significance at $P = 0.003$) to compensate for multiple comparisons. Following statistical correction, patients with RH were more likely to describe: Hard stools > 25% of the time, unable to evacuate despite urge > 25% of the time, incomplete emptying > 25% of the time, and straining and use of enemas or manual manoeuvres.

TABLE 8 – PATTERNS OF DEFAECATION IN CASES (RH) VS CONTROLS (NS).

Symptoms	NS N=668	RH N = 668	OR RH/NS	P-value
Symptoms associated with constipation				
Hard stools >25% of the time	344 (51%)	395 (59%)	1.4 (1.1-1.7)	0.006
Evacuation time >5 minutes	404 (60%)	428 (64%)	1.2 (0.9 – 1.5)	0.2
Unable to evacuate despite urge >25% of the time	337 (50%)	404 (60%)	1.5 (1.2 – 1.9)	0.003
Incomplete emptying >25% of the time	523 (78%)	569 (85%)	1.6 (1.2 – 2.1)	0.001
Sense of obstruction >25% of the time	375 (56%)	420 (63%)	1.3 (1.1 – 1.7)	0.01
Straining > 25% of the time	437 (65%)	498 (74%)	1.5 (1.2 – 2.0)	0.0003
Anal pain >25% of the time	365 (55%)	413 (62%)	1.3 (1.1 – 1.6)	0.009
Abdominal pain >25% of the time	390 (58%)	428 (64%)	1.3 (1.02 – 1.6)	0.03
Uses stimulant laxatives	106 (16%)	120 (18%)	1. (0.7 – 1.5)	1
Uses enemas or manual manoeuvres	287 (43%)	362 (54%)	1.6 (1.3 – 1.9)	<0.0001

TABLE 7. CONT.

Symptoms	NS N=668	RH N = 668	OR RH/NS	P-value
Symptoms associated with faecal incontinence				
Faecal urgency	349 (59%)	314 (53%)	0.8 (0.7 – 1.0)	0.06
Any form of faecal incontinence	436 (65%)	409 (61%)	0.84 (0.7 – 1.1)	0.14
Isolated solid incontinence	40 (6%)	49 (7%)	1.2 (0.8 – 1.9)	0.38
Isolated liquid incontinence	170 (25%)	163 (24%)	0.9 (0.7 – 1.2)	0.7
Both liquid & solid incontinence	226 (34%)	197 (29%)	0.8 (0.6 – 1.1)	0.1

As noted, there was no difference in overall rates of faecal incontinence between groups. When individual subtypes were examined, there was no difference in isolated forms of incontinence (liquid or solid).

11.3.3 Duration of symptoms

(Table 9)

The majority of constipation sufferers described symptoms for less than five years (37%). Patients with RH, however, were more likely than those with NS to describe a long history (greater than 20 years) of constipation (OR 1.5 [1.1 – 1.9]; $P = 0.004$).

TABLE 9 – DURATION OF SYMPTOMS IN PATIENTS WITH CONSTIPATION, CASES (RH) AND CONTROLS (NS)

Duration of symptoms	NS n = 459	RH n = 516	OR	p-value
Less than five years	175 (38%)	188 (36%)	0.9 (0.7 – 1.2)	0.59
5 – 9 years	88 (19%)	65 (13%)	0.6 (0.4 – 0.9)	0.006
10 – 19 years	65 (14%)	71% (14%)	0.96 (0.7 – 1.4)	0.9
> 20 years	131 (29%)	192 (37%)	1.5 (1.1 – 1.9)	0.004

11.3.4 Impact of bowel symptoms

Patients with RH were more likely to note that their bowel symptoms impacted on their life “a lot” compared with patients with normal sensation ($P = 0.001$) (Figure 34).

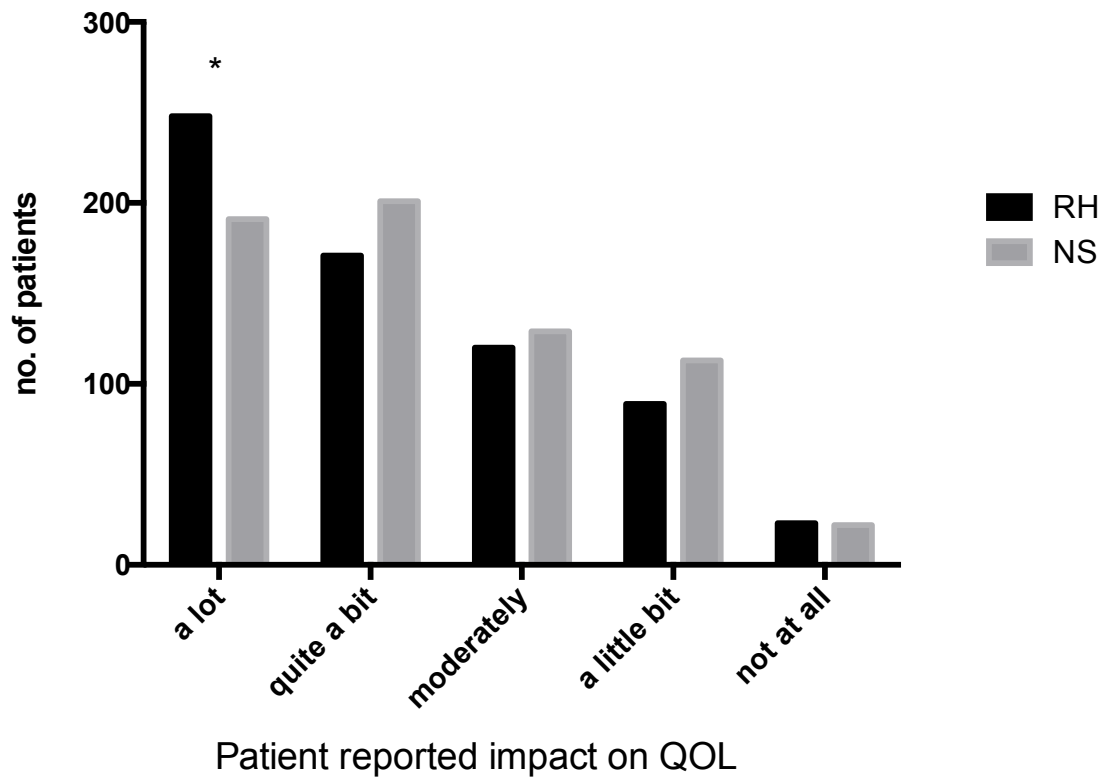


FIGURE 34 – PATIENT REPORTED IMPACT OF BOWEL SYMPTOMS ON QUALITY OF LIFE STRATIFIED BY SENSORY STATUS

(* P = 0.001)

11.3.5 Overall health status

Almost 50% of patients with NS described their health as well or very well compared with 43% of those with RH (P = 0.06). By contrast, nearly a quarter of patients with RH described their health as poor or very poor (RH = 24% vs. NS = 18%, P = 0.01). Patients with RH were almost twice as likely to report “very poor” health than controls (OR = 1.8 (95% CI = 1.1 – 2.8); P=0.01) (Figure 35).

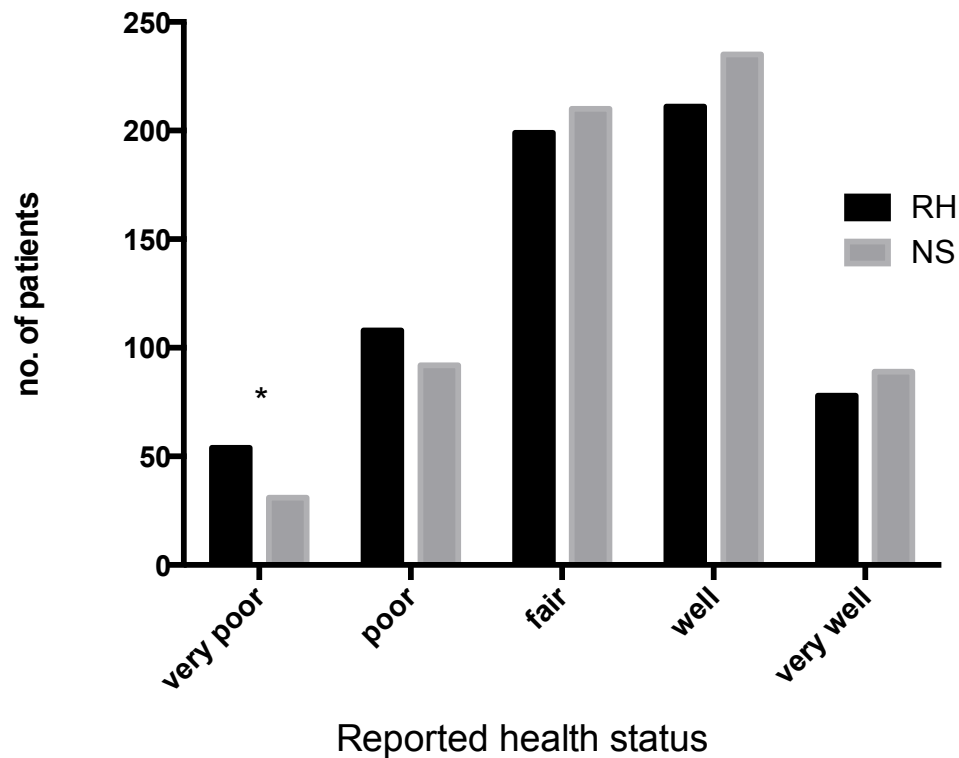


FIGURE 35 – PATIENT REPORTED HEALTH MEASURE STRATIFIED BY RECTAL SENSORY STATUS

PATIENTS WITH RH (BLACK) WERE SIGNIFICANTLY MORE LIKELY ($P = 0.01$) TO DESCRIBE VERY POOR HEALTH IN COMPARISON TO THOSE WITH NS (GREY).

11.3.6 Clinical significance of elevated rectal sensory thresholds.

A sub-analysis of patients with hyposensitivity was performed to determine if individual sensory thresholds were predictive of a more severe symptom phenotype. Data was reanalysed depending on whether patients had an elevated FCS threshold or normal FCS threshold, elevated DDV threshold or normal DDV threshold, and elevated MTV threshold or normal MTV threshold. Severity was determined by CCCS.

	Abnormal threshold	Normal threshold	P-value
FCS	N = 345 Median CCCS = 15 IQR = 9 - 20	N = 323 Median CCCS = 14 IQR = 9 - 19	0.03
DDV	N = 461 Median CCCS = 15 IQR = 9 - 20	N = 207 Median CCCS = 14 IQR = 9 - 18	0.07
MTV	N = 440 Median CCCS = 15 IQR = 9 - 19	N = 228 Median CCCS = 14 IQR = 9 - 20	0.39

Overall, median CCCS differed by only a single point (15 vs. 14) when defined by individual elevated sensory thresholds. First constant sensation was found to be statistically different although the clinical impact was small.

Further sub-analysis was thus conducted to determine if the number of elevated sensory thresholds (independent of the type of sensory threshold) predicted symptom severity. Patients with hyposensitivity were sub classified by the presence of one, two or three elevated sensory thresholds and compared with normosensitive patients (no elevated sensory thresholds). CCCS were compared between groups.

Patients with one, two or three elevated threshold all described higher rates of constipation (normal sensation = 68% vs. one threshold elevated (78%), two thresholds elevated = 75%, and three thresholds elevated = 80%; $P = 0.003$) than patients with normal rectal sensation. However, post hoc analysis revealed no difference in rates of constipation between those with one or more sensory thresholds elevated ($P = 0.42$) indicating that even the presence of one elevated sensory threshold confers increased risk of constipation.

All patients with elevated sensory thresholds (regardless of whether it was one, two or three) also scored higher on the CCCS than those with normal rectal sensation ($P < 0.0001$). However, those with three elevated thresholds scored significantly higher on the CCCS (three thresholds elevated = 17 (IQR 11 – 21) vs. two thresholds elevated and one threshold elevated = both 14 (9 – 19); $P = 0.003$), consistent with a more severe clinical phenotype.

In addition, patients with three elevated thresholds were twice as likely as others with RH to have a CCCS >20 (OR 3RH:RH = 2.1 [1.4 – 3.1], $P = 0.0005$) equating to more severe constipation.

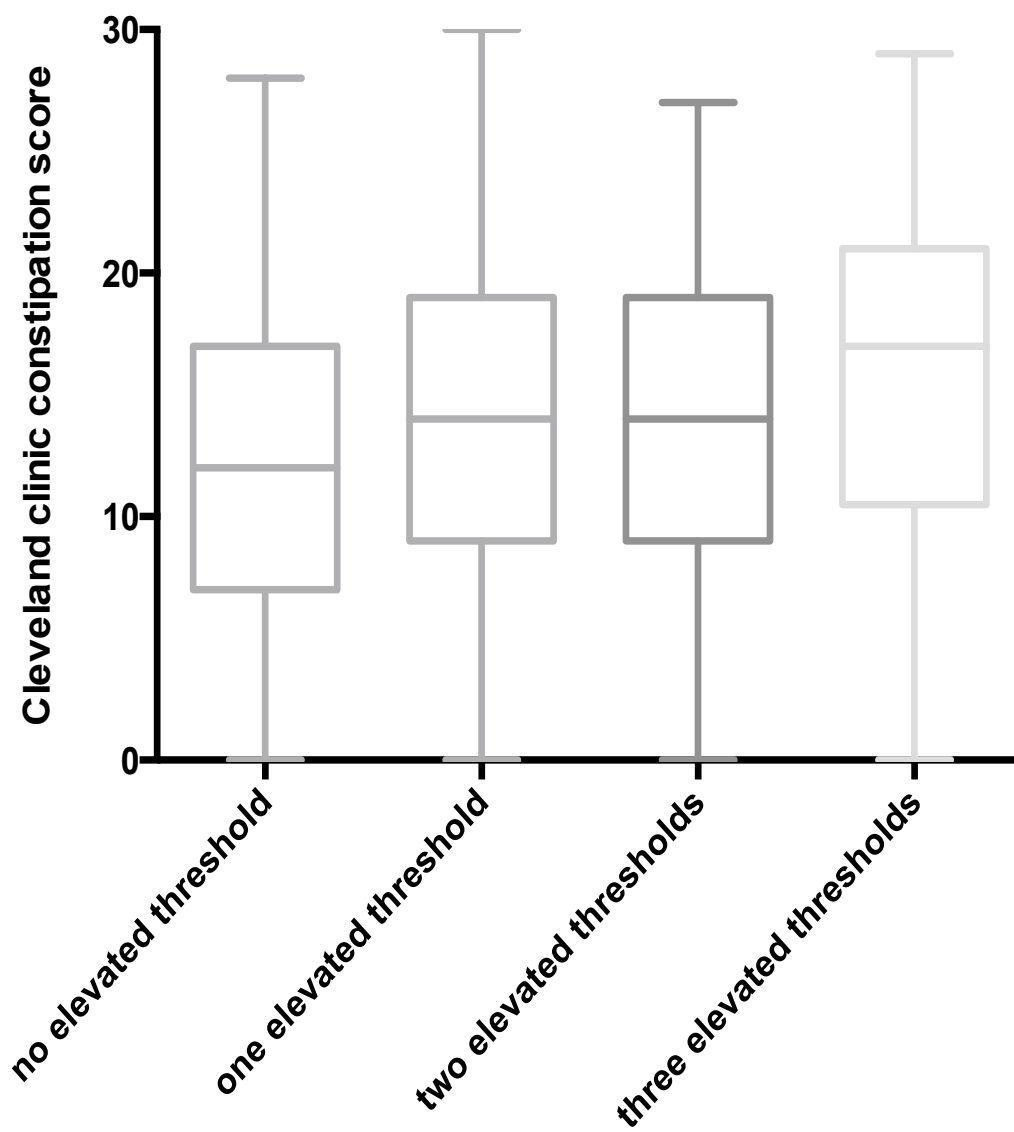


FIGURE 36 – CLEVELAND CONSTIPATION SCORE (MEDIAN [IQR], MIN, MAX) IN PATIENTS WITH NO ELEVATED SENSORY THRESHOLDS, ONE ELEVATED SENSORY THRESHOLD, TWO ELEVATED SENSORY THRESHOLD AND THREE ELEVATED SENSORY THRESHOLDS. ($P < 0.0001$)

11.3.7 Symptom Phenotype of Patients with Severe Rectal Hyposensitivity

(Table 10)

Further analysis was performed examining patients considered to have “severe” rectal hyposensitivity (all three sensory thresholds elevated: 3RH). One hundred and seventy-three patients fulfilled these criteria.

In comparison to all other patients with rectal hyposensitivity, those with “severe” RH described more frequently: marked defaecation infrequency (bowels open less than fortnightly) (severe RH = 10% vs. RH = 4% OR = 2.7 (1.4 – 5.4); $P = 0.005$), hard stools > 25% of the time ($P = 0.03$), painful motions > 25% of the time ($P = 0.02$) and the need for enemas or digitation ($P = 0.008$) (Table 10).

There was no difference in the frequency of symptoms otherwise classically associated with rectal evacuatory dysfunction such as: evacuatory time, need to strain, sense of obstruction to defaecation, incomplete emptying or inefficient evacuation (Table 10). There was no difference in the proportion of patients suffering abdominal pain. Patients with severe RH described a similar duration of symptoms as other patients with RH.

TABLE 10 – COMPARISON OF SYMPTOM FREQUENCY BETWEEN RH AND “SEVERE” RH

Symptoms	“Severe” RH N = 173	Other RH N = 495	OR	P - value
Symptoms of constipation				
Describes constipation	139 (80%)	337 (76%)	1.3 (0.8 - 1.9)	0.29
Hard stools >25% of the time	114 (66%)	281 (57%)	1.5 (1.02 – 2.1)	0.03
Evacuation time >5 minutes	120 (69%)	308 (62%)	1.4 (0.9 – 1.9)	0.1
Unable to evacuate despite urge >25% of the time	115 (66%)	289 (58%)	1.4 (1.0 – 2.0)	0.07
Incomplete emptying >25% of the time	154 (89%)	415 (84%)	1.6 (0.9 – 2.7)	0.1
Sense of obstruction >25% of the time	113 (65%)	307 (62%)	1.2 (0.8 – 1.7)	0.56
Straining >25% of the time	126 (72%)	398 (75%)	0.6 (0.9 -1.3)	0.6
Anal pain >25% of the time	120 (69%)	293 (59%)	1.6 (1.1 – 2.3)	0.02
Abdominal pain >25% of the time	119 (69%)	309 (62%)	1.3 (0.9 – 1.9)	0.1

Symptoms	“Severe” RH N = 173	Other RH N = 495	OR	P - value
Uses stimulant laxatives	28 (16%)	92 (19%)	1 (0.6 - 1.8)	1
Uses enemas or manual manoeuvres	109 (63%)	253 (51%)	1.6 (1.1 - 2.3)	0.008
Symptoms of incontinence				
Faecal urgency	84 (49%)	230 (54%)	1.1 (0.8 – 1.5)	0.65
Any form of faecal incontinence	106 (61%)	303 (61%)	1 (0.7 – 1.4)	1
Isolated solid incontinence	16 (9%)	33 (7%)	1.4 (0.8 – 2.7)	0.3
Isolated liquid incontinence	33 (18%)	130 (26%)	0.7 (0.4 – 1)	0.06
Both liquid & solid incontinence	57 (33%)	140 (28%)	1.2 (0.9 – 1.8)	0.2

There was no difference in incontinence rates (Table 10) between groups, and the severity of RH had no effect on SMIS (“other” RH median 8 [3 – 13] vs. “severe” RH median 8 [4 – 14]; $P = 0.59$). Severity of RH did not influence the reported impact of bowel symptoms on patient quality of life ($P = 0.61$) or, indeed, overall health status ($P = 0.82$).

11.4 Discussion

Implications of this study

This study is the first to systematically determine the clinical impact of RH using a large case-controlled series of patients presenting to a tertiary care centre with symptoms of bowel dysfunction. To summarise, the results show that:

- 1) Patients with RH are more likely to describe constipation as a presenting symptom,
- 2) Patients with RH describe a more severe constipation phenotype with a higher median CCCS than those with NS. A greater proportion of patients with RH also scored above 20 on the CCCS equating to severe symptoms,
- 3) Infrequency of defaecation, hard stools, sense of incomplete emptying, ineffective evacuation, sense of obstruction to defaecation, straining, painful defaecation / anal pain and abdominal pain were all more common in patients with RH compared to those with normal sensation,
- 4) Patients with RH reported a greater impact of symptoms on quality of life and poorer overall health status than those with normal sensation,
- 5) Patients with “severe” rectal hyposensitivity (i.e. all three sensory thresholds to latex balloon distension were elevated) had more severe constipation as measured by the CCCS, although there was

- no difference in constipation prevalence between “severe” patients and others with RH (one or two elevated sensory thresholds), and
- 6) There was no difference in incontinence prevalence or severity (determined via SMIS) of symptoms. Patients with RH were less likely to have isolated faecal incontinence (i.e. in the absence of constipation) than those with NS

Overall, these findings support anecdotal reports that have suggested that patients with RH are more likely to be constipated with a more severe clinical phenotype than patients with normal rectal sensation.

Sensory dysfunction and symptoms of constipation

RH is likely to impact on symptoms of constipation by a number of mechanisms. Certainly lack of, or inattention to, the urge to defaecate in response to normal rectal filling would account for the increased rates of infrequency in patients with RH. Equally, failure to appropriately respond to rectal distension would lead to impaction of the rectum, with the development of, in time, a large desiccated faecal bolus. Such a faecal mass would be difficult to pass, resulting in the increased frequency of symptoms consistent with rectal evacuatory dysfunction. Conversely, such symptoms could also be an effect of primary evacuatory failure, as patients with RH are known to have altered rectal contractility in response to distension (Schouten *et al.*, 1998) and higher rates of “functional” (poor propulsive force, failure of puborectalis or anal canal relaxation)

obstruction to defaecation (Gladman *et al.*, 2003b), suggesting a possible concurrent efferent / motor abnormality.

Overall, it is likely that cortical inattention and its subsequent effect on colonic physiology plays a major overriding role in each of the proposed scenarios above. This is supported by at least one study in healthy individuals which suggests constipation may be a learned phenomenon (Klauser *et al.*, 1990). This study showed that deliberate failure to respond to normal defaecatory urge resulted in decreased defaecation frequency with subsequent secondary effects on overall colonic motility leading to significantly reduced rectosigmoid and right colonic transit. Evacuated stool weight also decreased following voluntary suppressing of urge, although whether this was due to increased rectal impaction or decreased rectal filling overall is unknown. Unfortunately, Klauser *et al.* did not examine whether repeated voluntary suppression of defaecatory urge leads to subsequent sensory dysfunction on physiological examination. This would indeed be interesting to examine in subsequent studies using similar methodologies as described by Klauser *et al.* but also including assessment of rectal sensory function.

Spinal cord injured patients also provide an effective model when examining how RH affects colonic function. Such patients often have loss of sensory awareness of the viscera but intact local motor reflex function. In these circumstances, lack of cortical attention likely explains why

patients with supraconal spinal cord injuries (which otherwise have hypertonic rectal function (Krogh and Christensen, 2009) which would be expected to result in frequent defaecation / spontaneous evacuation) often describe evacuatory difficulties in addition colonic transit delay. Lack of urge may be overcome in such patients by using local stimulatory techniques like the insertion of a finger into the anal canal or suppositories (Krogh *et al.*, 1997) to bypass the need for higher centre control. Once defaecation is initiated, rectal evacuation can be completed via local reflex mechanisms (Lynch *et al.*, 2000). However, whether such studies can be generalised to all patients with constipation and RH in whom local motor reflex function may also be altered is unknown. Prolonged combined manometric and barostat studies in such patients during attempted defaecation may help delineate whether concurrent motor dysfunction is a significant contributing factor to symptom generation.

It is also apparent from the present study that sensory dysfunction is not the only mechanism responsible for the development of constipation. For instance, while patients with RH were more likely to describe constipation than those with normal sensation, two thirds of normosensitive patients also reported constipation. Such result highlights the difficulties of studying symptomatically defined conditions; by their very nature pathogenic mechanisms are often heterogeneous. This is further hampered by the considerable overlap of physiological abnormalities seen in patients with chronic constipation and RH. Previously, over 50% of patients with RH

have been shown to have concurrent physiological abnormalities such as slow transit or dyssynergic defaecation (Gladman *et al.*, 2003b). Whilst clearly the presence of such abnormalities are potential confounders (Gladman *et al.*, 2003b) when attempting to determine the clinical impact of sensory function, simply excluding such patients is not appropriate as, given the complex neurological feedback loops within the visceral nervous system, it is impossible to tease out to what degree the presence of RH itself is responsible for the existence of such additional physiological findings (i.e. RH may be implicated in the development of dyssynergic defaecation rather than simply an epiphenomenon). Defining a physiologically “pure” subject group is thus impossible. As a result, determining clinical, rather than statistically significant differences between groups is thus difficult. It could be argued that a rate of constipation of 69% for NS patients vs. 77% for RH patients, although statistically significant, is not clinically significant. After all both groups have high rates of constipation. However, given the heterogeneous nature of the disorder, the higher rates of constipation in the RH group suggest sensory dysfunction does influence the development of the condition providing important information as to the role of RH in the constipated population as a whole. The small clinical difference, however, means that the impact in individual patients remains less clear-cut and causation cannot be determined.

Sensory dysfunction and symptoms of incontinence

Previous epidemiological studies have noted an association with RH and faecal incontinence (Gladman *et al.*, 2003a), however in this study the presence of RH did not significantly impact on either the overall rates of incontinence or its severity. Furthermore, incontinence in RH patients was more commonly seen in the presence of constipation, with NS patients more likely to have isolated faecal incontinence than those with sensory dysfunction. This suggests that in patients with RH, sensory dysfunction may underlie faecal loading, contributing to symptoms of “overflow” or secondary incontinence.

Comparison to the literature

Despite repeated calls for a better understanding of the clinical impact of RH (Sloots and Felt-Bersma, 2003, Gladman *et al.*, 2006, Scott *et al.*, 2011), there is limited available data in the existing literature with which to compare this study. Gladman *et al.* reported the largest case series to date in 2003 (Gladman *et al.*, 2003a, Gladman *et al.*, 2003b). This work lacked a control group with normal rectal sensitivity, and specific symptoms of hindgut dysfunction and severity of presenting symptoms were not noted. However, presenting problem, comprehensive results of anorectal physiological testing and potential risk factors were all examined. This study presented results from 1681 patients seen within the Gastrointestinal Physiology Unit (the same institution as the present study) between 1994 and 2002, but approached the association of rectal

hyposensitivity and hindgut dysfunction from a different perspective. In this study data on consecutive patients presenting to the GI physiology unit for assessment of hindgut function was collected and divided into those with constipation alone, incontinence alone or both conditions. The proportion of patients with RH was then compared between clinical groups. Of these, 261 patients had RH to balloon distension (23%, 10% and 27% of patients with constipation alone, incontinence alone and both conditions respectively). Unfortunately, data regarding severity of constipation or incontinence symptoms was not collected. It is of interest to note that prevalence of RH at two different time points from different populations within the same institution were equivalent (1994 - 2002: 261/1681 [16%]; 2003 - 2012: 848/5204 [16%]). Subsequent results from Gladman *et al.* showed that, of the patients with RH, 48% described constipation, 27% incontinence and constipation, and 20% incontinence alone. This contrasts somewhat with the present study, which found higher rates of combined faecal incontinence and constipation at the expense of constipation alone. Rates of incontinence alone were similar (21%). It is likely that the observed difference was due to the implementation (subsequent to 2002) of a standardised questionnaire that, in every patient, inquired about symptoms of incontinence regardless of the reason for referral. This disparity suggests, that in a large number of patients, an inadequate clinical history is recorded perhaps with clinicians underestimating, under-reporting or simply not enquiring about symptoms of incontinence in patients presenting primarily with chronic constipation.

There are few studies focussed on the clinical impact of RH and indeed the present study is the first to show a clear association of RH with more severe symptomatology. Moving forward, it would be interesting to examine the association from the reverse direction, to determine if clinical phenotype predicts physiology. This could be achieved by assessing a subgroup of patients with constipation stratified by symptom score (mild, moderate and severe) to determine whether RH proportions differ. Starting with the clinical endpoint would provide further clarity as to the role that sensory dysfunction has in symptom generation. Such methodology would also allow the construction of ROC curves, which would be useful in confirming clinically relevant sensory threshold cut off values. In this study, while patients with RH were twice as likely than those with NS to have a CCCS > 20, indicating severe constipation, the majority of patients with RH still reported severity scores within the moderate range (CCCS = 8 – 20) and 10% of NS patients reported severe symptoms (CCCS > 20) indicating that present reference ranges may not be adequate. As discussed previously, however, the pathogenic heterogeneity of constipation as a condition does make such analysis difficult.

In contrast to RH, the role of rectal hypersensitivity in symptom development has been more thoroughly researched. The bulk of this literature is in patients with irritable bowel syndrome (Izquierdo *et al.*, 2005, van der Veek *et al.*, 2008, Sabate *et al.*, 2008, Castilloux *et al.*, 2008) and

faecal urgency / incontinence (Chan *et al.*, 2005c). In incontinence, hypersensitivity is associated with increased symptoms (stool frequency and urgency) and reduced quality of life. In the irritable bowel syndrome literature, the importance of rectal hypersensitivity as a biomarker for disease and as a hallmark of the condition is considered well established (Mertz *et al.*, 1995), with sensory abnormalities thought to be “critical to pathophysiology and symptom generation” (Mertz, 2003). There is emerging evidence that visceral sensitivity modulated by serotonin signalling is the critical physiological difference between patients diagnosed with IBS-C and chronic constipation (Shekhar *et al.*, 2013). For example, patients with IBS-C are more likely to be hypersensitive to rectal distension whereas those labelled chronic constipation are more likely to be hyposensitive. This is despite no other determinable differences in physiological investigations (Shekhar *et al.*, 2013) suggesting both conditions may be part of a spectrum of the same disorder with symptoms (or symptom reporting) influenced by sensory status. In the irritable bowel syndrome population, modulation of visceral sensitivity towards normality is likewise associated with symptomatic improvement (Poitras *et al.*, 2002). Frustratingly, when examining specific symptoms or overall severity of IBS symptoms, there are conflicting results (Izquierdo *et al.*, 2005, van der Veek *et al.*, 2008, Sabate *et al.*, 2008, Castilloux *et al.*, 2008). For instance, while hypersensitivity appears to be critical to the sensation of bloating (Agrawal *et al.*, 2008, Di Stefano *et al.*, 2011) and abdominal pain (Zar *et*

al., 2006), distinct phenotypic groups associated with hypersensitivity have not yet been established (Kuiken *et al.*, 2005).

Limitations

This study is, of course, limited by its design. While the data were collected prospectively, the analysis was carried out retrospectively which allows for the possibility of confounding by other variables not originally incorporated into the initial data collection. A direct link therefore, between RH and the causation of symptoms of constipation, cannot be truly established. Most frustratingly, whether RH is a primary pathology leading to symptoms or conversely whether chronic constipation itself results in the development of RH cannot be determined. However, despite these limitations, the clear association between RH and symptom severity, as well as evidence suggesting those with more severe RH have a more severe constipation phenotype, is compelling. Clearly rectal sensory function is of critical importance in patients with hindgut dysfunction.

It is conceded that the use of multiple comparison testing within the study also influences the confidence with which conclusions can be drawn. Reassuringly, when a conservative correction such as Bonferroni was applied to the analysis, patients with RH still have statistically significant increases in specific symptoms of constipation. Furthermore, the patterns of symptoms detected within the study were clinically appropriate and RH

was associated with worse global constipation symptom scores indicating the conclusions are clinically valid.

Unfortunately, whether the increase in symptom severity, decreased reported health status and increased negative impact of quality of life in patients with RH is an effect of a (patho)physiologically more severe condition, rather than simply heightened awareness of symptoms, cannot be determined. This is because of the potential for reporter bias; inherent within the study was a reliance on patients to adequately complete symptom questionnaires. As a result, the data is subjective in nature and has not been verified by an independent source. For instance, hypothetically, it may be possible that patients with RH over report severity of symptoms in comparison to those with normal sensation perhaps as a result of an, as yet, unknown and uncontrolled for variable (e.g. psychological factors, sexual abuse etc.) (North *et al.*, 1995, Guthrie *et al.*, 2004, Ringel *et al.*, 2004, Imhoff *et al.*, 2012).

Ongoing research

While this study has highlighted some clear clinical features that are associated with RH, the questionnaire did not enable information to quantify or qualify the urge to defaecate to be collected. This is clearly a critical issue in patients with sensory dysfunction. Certainly, rectal hypersensitivity has been shown to influence defaecation urge with a

significant increase in faecal urgency in patients with faecal incontinence (Chan *et al.*, 2005c). Patients with RH have also been shown, in at least one study with small numbers (Harraf *et al.*, 1998), to be more likely to have “no urge” constipation. It is fundamental therefore that ongoing research in this field establishes what is the normal urge for defaecation and the role of rectal sensation in its induction.

Although this study suggested RH might not be associated with faecal incontinence *per se*, the role of sensory dysfunction in patients with incontinence still warrants further research. Traditionally, continence is thought to be predominantly preserved by sphincter motor function, with dysfunction (and hence incontinence) occurring secondary to surgical or obstetric injury. In this study RH was shown to influence severity and prevalence of symptoms of constipation but not those associated with incontinence. This was despite over 60% of patients with RH describing a history of incontinence. Most commonly, in this group, incontinence occurred in conjunction with constipation (72% of the time) suggesting that in such patients, faecal incontinence may be a secondary phenomenon related to underlying faecal impaction. However, overall 17% of patients with RH still described isolated faecal incontinence, indicating rectal sensory function may well be important even in the absence of constipation. Undoubtedly it is possible that the impact of sensory function in incontinence has been overlooked in previous studies perhaps due to a dilution effect of the large number of women presenting with FI as a result

of obstetric injury. Given this, the impact of RH on FI may be better explored by examining a group of patients without a confounding history of sphincter trauma of injury.

Further research is also needed to determine if RH is an appropriate therapeutic target. While this study certainly confirms a strong association between RH and symptoms of constipation, it would be reassuring to demonstrate that therapies leading to normalisation of rectal sensory status in constipation (like that seen in the IBS literature (Poitras *et al.*, 2002)) results in improvement of symptoms. To date, a number of small studies (either using biofeedback (Rao *et al.*, 1997) or neuromodulation (Knowles *et al.*, 2012, Kang *et al.*, 2012)) have indicated that this appears to be the case, corroborating the findings of this study. Given the small number of subjects in such studies (maximum of 26 patients), larger scale studies however, are warranted.

11.5 Conclusions

This study is the first to determine in a large, age, sex and parity matched cohort of patients, the clinical impact of rectal hyposensitivity on hindgut dysfunction. Patients with RH described a more severe clinical phenotype of constipation, with a longer duration of symptoms and poorer quality of life. Specifically, patients with RH were more likely to describe infrequency of defaecation, hard stools, and symptoms of rectal evacuatory

dysfunction (straining, sense of obstruction, sense of incomplete emptying) than patients with normal sensory thresholds. Furthermore, patients with more severe sensory dysfunction had a more severe clinical presentation. This study highlights the critical importance of rectal sensory function on symptom development in patients with hindgut dysfunction. Further studies are justified to determine if normalisation of rectal sensation is an effective therapeutic target in such patients.

12 RECTAL HYPOSENSITIVITY ALLIED TO CO-EXISTENT CONSTIPATION IN MALES WITH FAECAL INCONTINENCE: AN UNDERAPPRECIATED PATHOPHYSIOLOGICAL MECHANISM.

12.1 Introduction

Traditionally, faecal incontinence (FI) is regarded as primarily a female condition, with the principal pathophysiological mechanism generally considered to be sphincter disruption secondary to obstetric injury (Kamm, 1994). This concept has recently been challenged however (Bharucha *et al.*, 2010), and in fact, female preponderance may be due to an over-representation of women presenting to specialist clinics rather than a true sex difference (Madoff *et al.*, 2004), as population studies show males and females are equally affected by incontinence. Overall, community studies have shown FI to have a prevalence of 3 – 7% (Whitehead *et al.*, 2009), distributed equally between the sexes, indicating that pathogenic mechanisms other than traumatic childbirth must be involved. Recent studies (Lunniss *et al.*, 2004, Kim *et al.*, 2008) have shown that a high number of men (up to 58%) with FI often have a past history of anal surgery (e.g. for haemorrhoids, fissure-in-ano, perianal sepsis etc.) suggesting sphincter disruption as a possible cause in males also. Nevertheless, it is known that up to 40% of men have no structural anal abnormalities on endo-anal ultrasound to explain their symptoms (Maeda *et al.*, 2009, Paramor *et al.*, 2014). Furthermore, men are also much more

likely than women to have no obviously identifiable risk factors (Lunniss *et al.*, 2004). Understanding aetiological mechanisms of FI in men is therefore critical.

While the association of FI and constipation is certainly well recognised in the paediatric and geriatric literature (Madoff *et al.*, 2004, Clayden and Wright, 2007), in adults this association has largely been overlooked. This is despite other population-based studies indicating that the presence of incomplete evacuation is an independent risk factor for FI (Bharucha *et al.*, 2010). Given that rectal sensory dysfunction (rectal hyposensitivity: RH) is known to be associated with constipation and particularly functional evacuatory disorders (Gladman *et al.*, 2003a) it is conceivable that RH, allied to defacatory dysfunction, is a contributing factor to the development of FI in a proportion of patients, both male and female. Nevertheless, because of the relative paucity of information available on the pathoaetiology of FI in males, this study will focus on men presenting consecutively to a tertiary centre for investigations of their symptoms.

To this end, this study has a number of aims:

1. to determine the clinical characteristics of men with faecal incontinence;
2. to determine the incidence of sphincter injury;
3. to determine the co-existence of constipation; and
4. to determine the impact of rectal sensory dysfunction.

12.2 Methods

A retrospective review of prospectively collected data was undertaken, selecting male patients presenting to a busy surgical tertiary referral unit for assessment of symptoms of FI over a five year period (2003 – 2008). Consecutive patients were included if data for both clinical symptom questionnaires and standard anorectal physiological investigations were complete. Questionnaires and investigations were those employed routinely in clinical practice within the department (as described in Chapter 10).

12.2.1 Clinical information

In all patients, data collected included patient demographics (age, sex, year of review), a detailed practitioner-directed history, including risk factors for FI (anorectal surgery, systemic neurologic disorder or spinal pathology) and predominant symptoms, as well as a completed comprehensive symptom questionnaire (Mohammed *et al.*, 2010) as described previously (Chapter 10). The questionnaire allowed calculation of previously validated scoring systems: the Cleveland Clinic constipation score (modified) (CCCS) (Agachan *et al.*, 1996a), and the St Mark's incontinence score (SMIS), (Vaizey *et al.*, 1999a) as previously described (Chapter 10). Patients were deemed to suffer from constipation if they reported a history of constipation when completing the symptom questionnaire.

12.2.2 Investigations

All patients underwent comprehensive anorectal physiological testing with the rectum unprepared (Chan *et al.*, 2005a) as described in Chapter 10. Several practitioners undertook these investigations, all adhering to a standardised method. All patients underwent:

1. station pull-through anal manometry;
2. endo-anal ultrasound;
3. assessment of rectal sensation; and
4. evacuation proctography.

12.2.3 Statistical analysis

Demographics, symptom scores, past medical histories and risk factors, co-existing symptoms and anorectal physiological test results were defined within the patient population. Symptom scores, symptom frequency, risk factors and anorectal physiological findings were compared between patients with RH or without (normal sensation: NS). Categorical statistical analysis was performed by a Fisher's exact test. For between groups analyses (i.e. symptom scores), a t-test, Mann-Whitney U test, or one-way ANOVA, depending upon Gaussian distribution, were utilised where appropriate. A *P* value of <0.05 was considered statistically significant. Analyses were performed using a commercially available statistical software package (Prism 5.0 GraphPad Software, San Diego, CA, USA).

12.3 Results

During the study period, 423 male patients were referred for investigation of faecal incontinence. The majority (305 patients) completed all anorectal physiology tests including proctography. One hundred and sixty of these patients completed their questionnaires in entirety, and therefore comprised the study cohort.

12.3.1 Characteristics of faecal incontinence in men

12.3.1.1 Presenting symptoms

(Table 11)

Although all 160 men complained primarily of FI, only 71 patients (44%) presented with FI alone. The majority described concurrent constipation, present in 75 patients (47%). Symptoms suggestive of prolapse were reported in 9%, unexplained anorectal pain in 7%, and prior “diagnosis” of irritable bowel syndrome in 4%, with several describing more than one condition.

Only 10 patients described isolated solid stool incontinence and sixty, isolated liquid stool incontinence. The remainder presented with a combination of liquid and solid stool incontinence (90/160: 56%). Sixty-seven (42%) patients described symptoms on a daily basis, most commonly with symptom duration of between one – four years. Seventy men (44%) described only faecal “smearing” of their underwear (which

previous studies (Titi *et al.*, 2007) have defined as “faecal leakage”), with the remainder suffering from “frank” faecal incontinence (56%).

With regard to the nature of the incontinence, 52% described passive incontinence alone, 14% urge incontinence alone, with 34% describing both symptoms (Table 11). Fifty-five percent of patients also described urgency with an inability to defer defaecation for greater than 5 minutes; 80% of these patients reported frank urge incontinence (associated involuntary loss of stool) on occasion. Overall mean St Mark’s incontinence score was 11 (IQR 7 – 15). Patients with passive incontinence had a lower median St Mark’s incontinence score (9 [IQR 5 - 13]) in comparison to those with urge incontinence (12 [IQR 6 – 15]; $P=0.04$). Patients with frank faecal incontinence reported higher scores (13 [IQR 9 - 15] than those reporting only faecal leakage (8 [IQR 5 - 12]; $P<0.0001$).

TABLE 11 – SYMPTOMS OF INCONTINENCE IN MALE PATIENTS.

Symptom	Study cohort (n=160)
Median age (range)	54 (16 – 85)
Passive incontinence alone	83 (52%)
Urge incontinence alone	23 (14%)
Passive and urge incontinence	54 (34%)
Faecal leakage (smearing of underpants only)	70 (44%)
Frank faecal incontinence (loss of whole motion)	90 (56%)
Faecal urgency	89 (55%)
Liquid stool incontinence only	60 (38%)
Solid stool incontinence only	10 (6%)
Daily incontinence episodes	67 (42%)
Episodes less than daily but more than once a week	29 (18%)
Episodes less than once a week but more than monthly	47 (29%)
Episodes less than once a month	8 (5%)
Frequency not defined	9 (6%)
Median St Mark's incontinence score (IQR)	11 (7 – 15)

12.3.1.2 Patterns of defaecation

12.3.1.2.1 Stool consistency

(Table 12)

Forty-four percent of patients described their predominant stool type as soft and formed (Bristol stool scale 3, 4 or 5). Thirty-six percent reported variable stool forms. Interestingly, only 13% of patients noted loose stools (Bristol scale 6 or 7), and only 7% described hard stools (Bristol scale 1 or 2). Stool consistency was not associated with a particular type of FI.

12.3.1.2.2 Frequency of defaecation

(Table 12)

Forty percent of patients described a normal defaecation frequency, opening their bowels every one to two days. A further 37% opened their bowels two to five times a day, with 14% of patients reporting marked frequency of defaecation opening their bowels more than five times a day. By contrast, infrequency of defaecation (i.e. less than 3 times a week) was rare, reported by only 6% percent of individuals. Abnormal frequency of defaecation was not associated with a particular type of incontinence ($p = 0.18$). There was no correlation between stool frequency and stool consistency.

TABLE 12 – FREQUENCY OF DEFAECATION AND CONSISTENCY OF STOOL IN MALE PATIENTS WITH FAECAL INCONTINENCE.

Symptom	Study cohort (n=160)
Hard stools (Bristol scale 1 or 2)	11 (7%)
Normal stool consistency (Bristol scale 3, 4, 5)	71 (44%)
Loose stools (Bristol 6 or 7)	21 (13%)
Variable stool consistency	57 (36%)
Infrequency of defaecation Less than once a fortnight	2 (1%)
Infrequency of defaecation Less than 3 bowel actions / week	8 (5%)
Bowels open 1 – 2 times every 1 – 2 days	64 (40%)
Bowels open > 2 - 5 times a day	59 (37%)
Bowels open greater than 5 times a day	23 (14%)

12.3.2 Risk factors for faecal incontinence in men

(Figure 37)

Overall, 40% of patients had undergone prior anal surgery, 14% abdominopelvic surgery, 22% reported prior back injury / surgery, 7% had diabetes, 11% had a systemic neurological disorder (including Parkinson's disease and multiple sclerosis), and 2% had undergone pelvic irradiation, with many reporting more than one prior risk factor. Nevertheless, there was no identifiable risk factor in almost 40%. In terms of attribution, only 55 patients (34%) assigned the onset of symptoms to a clear precipitant, most commonly anal surgery (29 patients).

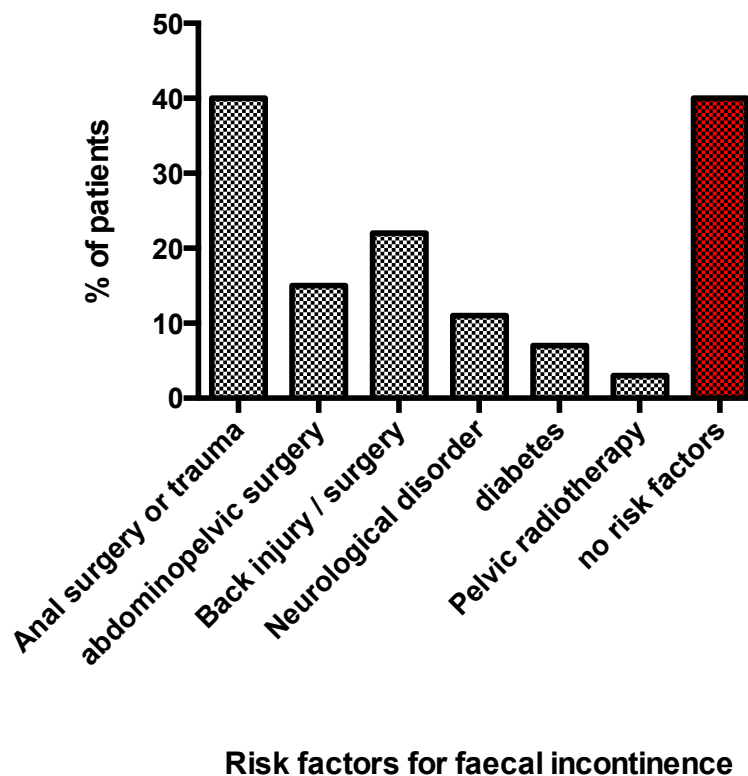


FIGURE 37 – PERCENTAGE OF PATIENTS WITH PRIOR IDENTIFIED RISK FACTORS FOR FAECAL INCONTINENCE.

PATIENTS WITH NO RISK FACTORS (40%) HIGHLIGHTED IN RED.

12.3.3 Association of faecal incontinence with symptoms of constipation and rectal evacuatory dysfunction

(Table 13)

As previously described, 47% of incontinent males reported co-existent constipation. Of the constipated patients ($n = 75$), onset of constipation was between one and five years ago in 35%, more than ten years ago in 33%, and within the last year in 9%. As noted previously, reported frequency of hard stools and infrequency of defaecation was low (Table 12) with symptoms of evacuatory dysfunction predominating.

Fifty-eight percent of patients reported a sense of incomplete rectal evacuation after defaecation more than 25% of the time, with almost half of these reporting a sense of obstruction to defaecation; furthermore, 26% of patients strained at stool more than 25% of the time. Eight percent of patients required manual assistance (digitation) to aid faecal expulsion, and 10% reported unsuccessful evacuatory attempts more than 25% of the time. Nine percent noted a toileting time of greater than 30 minutes. Twenty-four percent of patients reported taking laxatives. Even though 85 patients denied constipation, 61 of such patients described at least one symptom associated with constipation and 33 patients had a Cleveland constipation score (CCCS) of 8 or more, consistent with significant constipation. Only 24 patients (15%) denied any symptoms of constipation.

The mean CCCS was 10 (IQR = 6 – 13). There were no differences in overall reported incidence or severity (as determined by CCCS) of constipation between subgroups of patients according to type of incontinence.

TABLE 13 – SYMPTOMS OF CONCURRENT CONSTIPATION IN MALES WITH FAECAL INCONTINENCE.

VALUES GIVEN AS TOTAL NUMBER AND PERCENTAGE OF TOTAL STUDY COHORT.

Symptom	Study cohort (n=160)
Self-reported constipation	75 (47%)
Median (IQR) Cleveland Clinic constipation score all patients	10 (6 – 13)
Median (IQR) Cleveland Clinic constipation score in patients self reporting constipation	14 (11 – 18)
Reported loss of the call to stool	12 (7%)
Unsuccessful evacuatory efforts >25% of the time	17 (10%)
Sense of incomplete emptying >25% of the time	93 (58%)
Need to strain >25% of the time	42 (26%)
Sense of obstruction >25% of the time	45 (28%)
Prolonged defaecation >30 mins	14 (9%)
Digital assistance	13 (8%)
Painful defaecation	38 (24%)

Symptom	Study cohort (n=160)
Abdominal pain	42 (26%)
Bloating	13 (8%)
Laxative use	38 (24%)
No symptoms of constipation	23 (15%)

12.3.4 Anorectal findings in males with faecal incontinence

12.3.4.1 Anal sphincter integrity and function

(Table 14)

Overall, 38 patients (24%) had structural damage to at least one sphincter muscle, of whom the majority (66%) described a past history of anal surgery. Endo-anal ultrasound revealed internal anal sphincter disruption in 27 of these patients and external anal sphincter disruption in 15. In four patients, both sphincters were compromised. A further 35 (22%) patients had a functional sphincter deficiency on manometry (17 reduced resting pressure alone, 13 reduced anal squeeze increment pressures alone, and five both pressures reduced), despite intact sphincters on ultrasound. Of these patients, only 25% (n = 8) had undergone prior anal surgery.

TABLE 14 – ANAL SPHINCTER MORPHOLOGY AND FUNCTION, DETERMINED BY MANOMETRY AND ENDOANAL ULTRASOUND.

VALUES GIVEN AS TOTAL NUMBER AND PERCENTAGE OF STUDY COHORT

Possible cause for FI	Study cohort (n=160)
IAS disruption	27 (17%)
EAS disruption	15 (9%)
Both IAS and EAS disruption	4 (3%)
Anal resting pressure <50 cmH ₂ O	39 (24%)
Anal squeeze increment <50 cmH ₂ O	29 (18%)
Sphincter (IAS or EAS) disruption with abnormal sphincter pressure	19 (12%)
Sphincter (IAS or EAS) disruption with normal sphincter pressure	19 (12%)
Sphincters intact with abnormal sphincter pressure	35 (22%)

Overall, 45% of patients had either structurally or functionally incompetent anal sphincters as a possible cause for their incontinence. However, the remaining 55% of the cohort had what was considered normal sphincter anatomy and function.

12.3.4.2 Proctographic results in patients with faecal incontinence

(Table 16)

Despite presenting primarily with faecal incontinence, 48 patients (30%) had impaired rectal evacuation on proctography, with 22 patients having

prolonged defaecation and 39 patients incompletely evacuating the rectum (13 patients had both). In these 48 individuals, the cause of disturbed evacuation was 'functional' in 36 (i.e. inadequate opening of the anorectal angle; prominent impression of puborectalis throughout; poor relaxation of the anal canal; poor expulsive effort generated), and 'mechanical' in 12 individuals (i.e. Secondary to intussusception, enterocoele etc).

12.3.4.3 Rectal sensation

(Figure 38)

Overall, median first sensation volume was 50 ml (range 15 – >360), defaecation desire volume was 120 ml (20 – >360) and maximal tolerable volume was 180 ml (60 – >360). One hundred and thirty-two (82%) patients had normal rectal sensation (NS), 26 (17%) had rectal hyposensitivity, and 2 (1%) had rectal hypersensitivity (Figure 1).

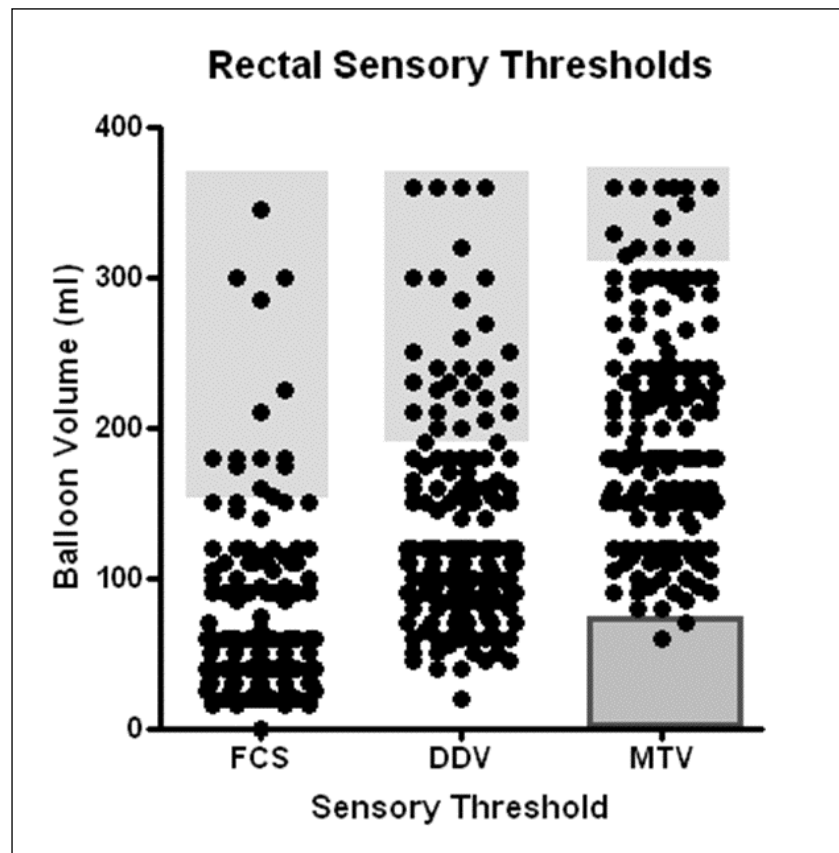


FIGURE 38 – SCATTER PLOT OF RECTAL SENSORY THRESHOLDS TO LATEX BALLOON DISTENSION.

FCS = FIRST CONSTANT SENSATION, DDV = DEFAECATORY DESIRE VOLUME AND MTV = MAXIMAL TOLERABLE VOLUME. GREY SHADING INDICATES RECTAL HYPOSENSITIVITY, GREY OUTLINED BOX INDICATES RECTAL HYPERSENSITIVITY.

12.3.5 Association between RH and constipation

(Table 15, Table 16)

Sensory status did not appear to impact on the type or severity of faecal incontinence. There were no specific symptoms that significantly differed between the groups stratified by sensory status. However, the incidence of constipation in patients with RH was significantly greater than in patients with NS (77% vs. 40%; $P=0.001$), with higher rates of infrequency

($P=0.003$), unsuccessful evacuatory efforts ($P=0.008$), and sense of incomplete rectal evacuation ($P=0.002$) reported. Incontinent men with RH also more commonly used laxatives ($P=0.02$) and there was a trend for men with RH to report “loss of the call to stool” (Table 8). Overall, patients with RH had higher constipation scores than patients with NS (RH: median 13 [IQR: 8 - 17] vs. NS: 9 [5 - 13]; $P=0.004$) but no difference in incontinence scores (RH: 12 [8 - 14] vs. NS: 11 [7 - 15]; $P=0.62$).

TABLE 15 – NUMBERS OF INCONTINENT PATIENTS REPORTING SYMPTOMS OF CONSTIPATION IN THOSE WITH NORMAL RECTAL SENSATION (NS), AND THOSE WITH RH. COMPARISON OF TYPE OF INCONTINENCE, STRATIFIED BY SENSORY SUBGROUPS

Symptom	NS (n=132)	RH (n=26)	P value
Median age (range)	54 (16 – 75)	49 (16 – 85)	0.27
Passive incontinence alone	68 (51%)	14 (54%)	1.0
Urge incontinence alone	18 (14%)	4 (15%)	0.76
Passive and urge incontinence	46 (32%)	8 (27%)	1.0
Fecal urgency	72 (55%)	15 (58%)	0.83
Median St Mark’s incontinence score (IQR)	11 (7 – 15)	12 (8 – 14)	0.62
Self-reported constipation	53 (40%)	20 (77%)	0.001
Median Cleveland Clinic constipation score (IQR)	9 (5 – 13)	13 (8 – 17)	0.004

Symptom	NS (n=132)	RH (n=26)	P value
Infrequency of defaecation <3 bowel actions / week	3 (2%)	5 (19%)	0.003
Hard stools (Bristol scale 1 or 2)	9 (7%)	2 (8%)	1.0
Normal stool consistency (Bristol scale 3, 4, 5)	61 (46%)	10 (38%)	0.5
Loose stools (Bristol 6 or 7)	18 (14%)	3 (12%)	1.0
Variable stool consistency	44 (33%)	11 (42%)	0.64
Loss of the call to stool	7 (5%)	5 (15%)	0.08
Unsuccessful evacuatory efforts >25% of the time	10 (8%)	7 (27%)	0.008
Sense of incomplete emptying >25% of the time	72 (55%)	19 (73%)	0.13
Sense of incomplete emptying 100% of the time	27 (20%)	13 (50%)	0.002
Need to strain >25% of the time	32 (24%)	10 (38%)	0.15
Prolonged defaecation >30 mins	12 (9%)	2 (8%)	1.0
Digital assistance	10 (8%)	3 (12%)	0.450
Sense of obstruction >25% of the time	33 (25%)	10 (38%)	0.15
Painful defaecation	31 (23%)	6 (23%)	1.0
Abdominal pain	30 (23%)	10 (38%)	0.14
Bloating	9 (7%)	4 (15%)	0.23
Laxative use	26 (20%)	11 (42%)	0.02

With regard to risk factors, patients with RH had higher rates of diabetes in comparison to patients with NS (19% vs. 5%; $P=0.03$), and there was a trend toward an increased incidence of a systemic neurological disorder (23% vs. 9% in NS; $P=0.08$).

Notably, anal sphincter dysfunction (reduced pressures on manometry, but with structurally intact sphincter muscles) was significantly more common in patients with RH when compared to patients with normal rectal sensation (42% vs. 18%; $P=0.02$: Table 10).

TABLE 16 – ALLIED PHYSIOLOGICAL AND ANATOMICAL FINDINGS AS STRATIFIED BY RECTAL SENSORY STATUS

Measure	NS (n=132)	RH (n=26)	P value
IAS disruption	24 (19%)	3 (15%)	0.57
EAS disruption	14 (11%)	1 (8%)	0.47
Both IAS and EAS disruption	4 (3%)	0 (0%)	1.0
Anal resting pressure <50 cmH ₂ O	31 (23%)	8 (30%)	0.46
Anal squeeze increment <50 cmH ₂ O	21 (16%)	8 (30%)	0.09
Sphincter (IAS or EAS) disruption Abnormal sphincter pressure	17 (13%)	2 (8%)	0.74
Sphincter (IAS or EAS) disruption Normal sphincter pressure	17 (13%)	2 (8%)	0.75
Sphincters intact Abnormal sphincter pressure	24 (18%)	11 (42%)	0.02
Prolonged evacuation on proctogram >180 sec	13 (10%)	9 (35%)	0.02

Measure	NS (n=132)	RH (n=26)	P value
Incomplete evacuation on proctogram <55%	26 (20%)	13 (50%)	0.02
Total number of patients with evacuatory dysfunction	34 (26%)	14 (54%)	0.008
Functional obstruction to defaecation	25 (19%)	11 (42%)	0.02
Mechanical obstruction to defaecation i.e. intussusception	9 (7%)	3 (12%)	0.4
No physiological cause for incontinence found	58 (44%)	3 (12%)	0.001

Patients with rectal hyposensitivity were significantly more likely to have rectal evacuatory dysfunction (26% vs. 54%; $P=0.008$) on proctography as evidenced by prolonged defaecation (10% vs. 35%; $P=0.02$) and incomplete evacuation (20 vs. 50%; $P=0.02$). In patients with sensory dysfunction this was most commonly as a result of a “functional” obstruction (poor propulsive force, dyssynergic defaecation etc.) (19% vs. 42%; $P=0.02$) rather than mechanical obstruction.

12.4 Discussion

In contrast to the substantial body of literature implicating anal sphincter dysfunction as the principal mechanism for FI in females (Kamm, 1994, Lunniss *et al.*, 2004), this study has demonstrated that only a minority of men with FI have such pathology. In females, it is understood that the cause of sphincter trauma is most commonly obstetric, with 23 – 45% of

primigravidas having sonographic evidence of sphincter damage following delivery (Lunniss and Scott, 2007). By contrast, in males who have sphincter injury, this study and others (Lunniss *et al.*, 2004, Kim *et al.*, 2008) indicate that their sphincter damage is primarily iatrogenic. However 40% of males have no discernible risk factors for their symptoms and therefore alternative pathoaetiologic mechanisms for the development of FI in men must be considered.

A striking finding of this study is that co-existent symptoms of constipation and rectal evacuatory dysfunction (RED) are common in males presenting with FI. Furthermore, impaired rectal sensation (RH) was found in one-sixth of patients and was associated with more severe RED, both symptomatically and physiologically. This finding thus implicates suprasphincteric mechanisms in the pathophysiology of FI in adult males. Further, it is possible (given the strong association of RED and constipation) that FI may be a secondary phenomenon, especially in the presence of rectal sensory dysfunction.

Constipation as a possible contributor to the development of FI has been relatively overlooked in the adult literature. This is, in part, because previous studies have focused on women, and also because, arguably, disproportionate attention has been paid to the consequences of obstetric-related trauma to the anal sphincters since the advent of endo-anal ultrasound. This is despite “overflow incontinence” secondary to

constipation being accepted as the major underlying cause for FI in both geriatric, (Ryan *et al.*, 1974, Johanson *et al.*, 1997) and paediatric populations (up to 95% of children with encopresis are found to be constipated) (Clayden and Wright, 2007). In this study, almost 50% of men described themselves as constipated, with 30% having evidence of evacuatory dysfunction on proctography and a further 6% describing infrequency or hard stools. It is worth noting that a small proportion of patients (12%) claimed to be constipated, although they denied hard or infrequent stools and had normal evacuation at proctography, suggesting that psycho-behavioral factors also play a part in symptom generation.

FI as a consequence of underlying constipation is hypothesised to result from three principal mechanisms: (1) “overflow”, secondary to faecal impaction, may lead to FI due to liquid stool seeping around an intra-rectal bolus of solid stool, or via the production of large volumes of mucus; (2) secondary to a rectal evacuatory disorder, either mechanical or functional (especially dyssynergic defaecation), with residual rectal stool resulting in inhibition of the reflex contraction of the anal sphincter muscles and the development of a more obtuse rectal angle; and (3), by the development of pelvic floor weakness, secondary to chronic straining, through traction neuropathy of pudendal and pelvic nerves, (Nurko and Scott, 2011). Unfortunately, determination of pudendal nerve latencies was not technically possible in almost half of the study cohort, and thus these results are not presented. However, neuropathy may explain those

reduced anal pressures observed, despite sphincter integrity (Gooneratne *et al.*, 2007). It may also be argued that the simple endosonographic classification used in this study (intact / disrupted) fails to acknowledge thinning or atrophy of the sphincter muscles, and this may also contribute to the discrepancy in observed frequencies of morphological and functional disturbances.

Rectal hyposensitivity is found most commonly in patients with co-existing FI and constipation (Gladman *et al.*, 2003a) and in this study, its presence is highly suggestive of co-existent constipation. RH, however, did not appear to significantly influence either the type or severity of incontinence. The association of RH is consistent with the three hypotheses outlined above. RH, either via true afferent dysfunction, rectal hypercompliance, or increased rectal capacity, can result in faecal retention due to a lack of awareness of rectal fullness (or emptiness) (Gladman *et al.*, 2009). The highly significant association of RH and functional outlet obstruction reinforces the concept (Rao *et al.*, 2004b, Gladman *et al.*, 2006) that intact rectal sensation is required for recto-anal coordination and relaxation of the pelvic floor during defaecation. This study has also shown that RH is associated with impaired anal sphincter function, without sphincter disruption; this may be attributed to a combination of pelvic floor denervation, persistent reflex inhibition of the internal anal sphincter and, together with decreased anal sensation, failure of conscious contraction of the external anal sphincter. Such a combination of factors would allow for

leakage of stool (Read and Abouzekry, 1986, Nurko and Scott, 2011). In addition, diabetes was more prevalent amongst patients with RH, and there was a trend towards an increased frequency of other neurological disorders, suggestive of a more generalised underlying neuropathy.

The very low prevalence of rectal hypersensitivity within this study cohort is surprising, and at odds with other studies which have reported rates up to 40%. Importantly, however, such studies have principally addressed females (Chan *et al.*, 2005a, Andrews *et al.*, 2007), and the discrepancy is likely to reflect the high rates of obstetric-related injury in women, where rectal hypersensitivity has been hypothesised to be a secondary phenomenon related to the underlying sphincter defect (Chan *et al.*, 2005a).

At the time of writing, and to the authors' knowledge, this is the largest cohort of male patients with FI in whom past medical history, symptoms scores and anorectal physiology have been prospectively collected. This has allowed characterisation of the clinical features of male incontinence as well as the assessment of any associated clinical symptoms such as those associated with constipation. When comparing these results to prior literature, a previous observational study, performed by Kim *et al* in 2008, (Kim *et al.*, 2008) relied on retrospective chart review to examine possible precipitants for FI, and clinical and physiologic findings were not characterised. Another study by Titi *et al.* (Titi *et al.*, 2007) examined

physiological features in males with incontinence, but little attention was paid to clinical features. Notably, patient populations differed between these two studies. In the present study cohort, only 11% of men, compared to 50% in Kim *et al.*'s study, were over the age of 70. This is perhaps because our cohort was selected through a tertiary referral clinic within a surgical department, to whom more infirm elderly patients may not be referred. Study outcomes also differed from the study by Titi *et al.*, (Titi *et al.*, 2007) who concluded that FI was due to impaired sphincter function, as men with FI had lower sphincter pressures than healthy individuals and those with anal leakage alone. Despite Titi's *et al.*'s conclusions, more detailed examination of the study revealed that, despite patients with FI having overall lower sphincter pressures, the majority of sufferers actually had sphincter pressures within the normal range, and only five men had sphincter defects on ultrasound. More recently Paramor *et al.* (Paramor *et al.*, 2014) also studied 100 men with FI and found that in comparison to females with a similar severity of incontinence, males were more likely to have normal anal resting and squeeze pressures. This is consistent with the results of the current study.

Interpretation of the results of this study requires acknowledgement that all patients were recruited at tertiary care level and hence may be at the more severe end of the disorder. Whether the results can therefore be extrapolated to the wider population of males with FI, the majority of whom appear not to seek medical help (given the differences in prevalence in

population versus cohort studies), is unclear. The current study is also limited by its design such that only clinical associations rather than causation can be demonstrated. There is also the potential for recruitment bias, in that only patients in whom information was complete (questionnaire and physiologic test results) were included; such patients may have had the perception of more troubling symptoms than those for whom information was incomplete.

The association of constipation and incontinence has important management implications, as treatment strategies to manage evacuatory dysfunction may obviate the need for therapies directed primarily at FI. Furthermore, attempts at surgical restoration of continence are frequently associated with the unmasking of a covert, or worsening of an existent evacuatory disorder (Malouf *et al.*, 2000). Historically, proctography has only been recommended in the small proportion of patients with FI who complain of overt evacuatory symptoms (Diamant *et al.*, 1999, Madoff *et al.*, 2004, Chatoor *et al.*, 2007). However, the evidence base for this is primarily derived from studies in women and this study certainly strengthens the argument that proctography (or other test of evacuatory function) should also be performed routinely as part of the primary investigation of faecal incontinence.

12.5 Conclusions

In summary, this study reveals that among adult men referred to a tertiary surgical unit for investigation of their fecal incontinence, rectal evacuatory dysfunction and impaired rectal sensation are present in a significant proportion. Appropriate history taking, including presence and type of any constipation symptoms, and physiological assessment, including rectal sensitivity testing and evacuation proctography, should be routine. Whether the results of this study are transferable to the management algorithm of females with fecal incontinence merits further research. Targeted treatment, based on a comprehensive understanding of symptomatology and pathophysiology, is paramount in this era of increasing use of surgery for functional colorectal disorders.

13 RECTAL HYPOSENSITIVITY IS ASSOCIATED WITH SPECIFIC CHANGES IN PATTERNS OF SENSATION ASSOCIATED WITH THE URGE TO DEFAECATE

13.1 Introduction

In health, rectal evacuation relies on a coordinated series of events involving multiple physiological, anatomical and neural components, and is dependent on a complex interplay between motor and sensory domains. Although defaecation itself is thought to commence with the development of specific pre-defaecatory colonic motor activity (Dinning *et al.*, 2004), the role of sensation is integral. It is believed that for any individual, defaecation starts with an urge (sensation) of wanting to do so and a considerable body of information indicates that this sensation primarily originates in the colorectum (Broens *et al.*, 1994, Bampton *et al.*, 2000, Palit *et al.*, 2012a). Intermittent filling of the rectum, as a result of propagating colonic waves, produces the perception of rectal fullness via stimulation of rectal afferent pathways through distension of the colorectum. These sensory stimuli (though perhaps sub-cortical) trigger relaxation of the internal anal sphincter through the recto-anal inhibitory reflex, allowing 'sampling' of intraluminal contents (Palit *et al.*, 2012a) by the sensitive anal mucosa. If circumstances are socially acceptable, defaecation may then occur. Rectal sensory dysfunction, be it heightened or blunted, has the clear potential for compromise of either evacuatory

function or faecal continence, resulting in definable symptoms and clinical syndromes.

Heightened rectal sensation or rectal hypersensitivity has been extensively studied (Mertz *et al.*, 1995, Poitras *et al.*, 2002, Camilleri, 2002, Farmer and Aziz, 2009) and is considered a biomarker for functional gastrointestinal disorders such as the irritable bowel syndrome (Mertz, 2003). By contrast, the role of blunted rectal sensation (rectal hyposensitivity (RH)) is less well established.

Despite being frequently observed on testing, the role of rectal hyposensitivity in the pathogenesis of hindgut conditions remains poorly understood (Burgell and Scott, 2012). While a small number of studies have attempted to determine the aetiology and / or risk factors for RH (Gladman *et al.*, 2003b, Gladman *et al.*, 2005, Gladman *et al.*, 2009), few have examined the clinical significance of the physiological finding of RH. Anecdotal evidence, as well as a handful of studies examining visceral sensation in the irritable bowel syndrome, suggests that patients with RH have an altered or attenuated “call to stool” (Harraf *et al.*, 1998, Agrawal *et al.*, 2008), although this has not been robustly tested.

This study aimed to determine the normal sensory patterns associated with defaecation, as well as assessing the impact of rectal sensory

dysfunction on the urge to defaecate and success of defaecation, to help define the clinical impact of rectal hyposensitivity.

13.2 Methods

13.2.1 Patients and controls

Prospective collection of data was undertaken, selecting female patients presenting to a large tertiary referral unit for assessment of symptoms of chronic constipation over a one year period (2012). Chronic constipation was defined as “unsatisfactory defaecation characterized by infrequent stools, difficult stool passage or both, at least for the previous three months” as per the American College of Gastroenterology Chronic Constipation Task Force guidelines (American College of Gastroenterology Chronic Constipation Task Force, 2005a). Patients were included if data for viscerosensory questionnaires (see below) were complete. This questionnaire is routinely employed in clinical care within the unit in which the study was conducted.

All patients also underwent comprehensive anorectal sensation testing as described in Chapter 10 as part of their standard clinical diagnostic workup. Clinical history and risk factors for hindgut dysfunction (i.e. obstetric injury, spinal injury, prior surgery etc.) were also obtained at the time of physiological assessment. Patients were stratified into sensory subgroups based on the results of latex balloon distension of the rectum. Patients

were defined as hyposensitive if sensory thresholds were raised beyond the normal range (Chapter 10), or hypersensitive if maximal tolerable sensation was less than 80 mls, as defined previously (Chapter 10).

Healthy volunteer data were obtained for comparison through subjects participating in other physiology-based research studies running concurrently within the institution in which the study was conducted. Each study was approved by the City and East London Ethics Committee / Queen Mary, University of London ethics committee (REC numbers QMREC 2012/13, 10/H0704/11). Healthy volunteers completed the sensory questionnaire but did not undergo anorectal physiological testing.

13.2.2 Viscerosensory questionnaire

The specialised viscerosensory questionnaire has previously been developed to specifically assess perception of the “call to stool” in relation to bowel habit and is included in the clinical assessment of patients with hindgut dysfunction although as yet, has not been formally validated. It includes assessment of: 1) presence or absence of the urge to defaecate; 2) the location of the sensation for the urge to defaecate; determined by shading an area on a stylised image (Figure 39); 3) quality of sensation of the urge to defaecate, by circling pre-defined word triggers (derived from a previous pilot study run within the unit), or by providing free text description; 4) strength of the urge to defaecate as per a visual analogue scale anchored 0 – 10 (no sense of urge to extreme urgency); 5) stool

consistency as per the Bristol stool chart (Lewis and Heaton, 1997); and 6) completeness of defaecation also by visual analogue scale (also 0 – 10, nil evacuation to complete evacuation). A maximum of five bowel actions were described over a five-day period.

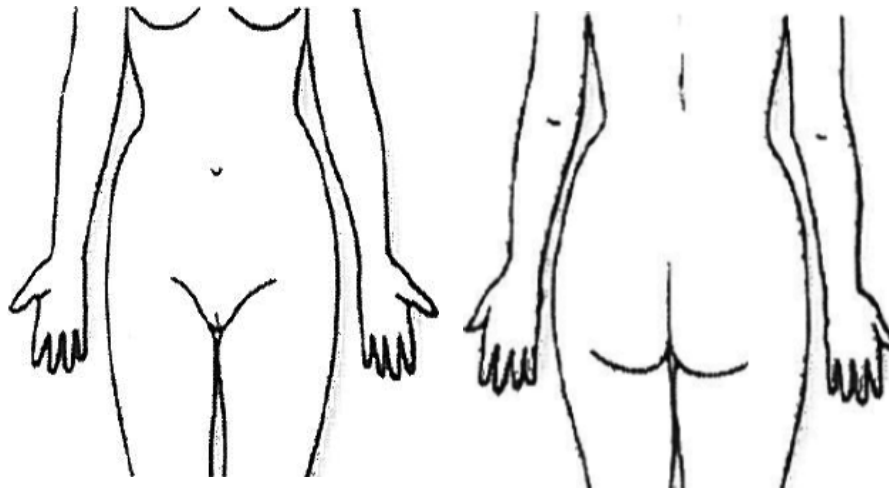


FIGURE 39 – STYLISTED IMAGES ON WHICH PATIENTS INDICATED THE AREA ASSOCIATED WITH THE URGE TO DEFAECATE

After digitising images, the area in which sensation of the urge to defaecate was located was described in three ways: firstly the location (front, back, both, neither) was defined; secondly, the centre (X & Y pixel co-ordinates) of the shaded area was noted; finally the overall area in which sensation was experienced was determined (see below).

13.2.3 Data analysis

13.2.3.1 Analysis of location and area of sensation

The images were digitised using ImageJ open source software (rsbweb.nih.gov/ij/). All images were resized to a constant; the area of sensation was highlighted and converted to a text file which, using MATLAB signal processing toolbox (The Math Works, Natick, MA, USA), was collated and converted to a cumulative image by summing the location of each shaded pixel for all subjects to produce a colour scaled frequency of sensation / area map (Figure 40).

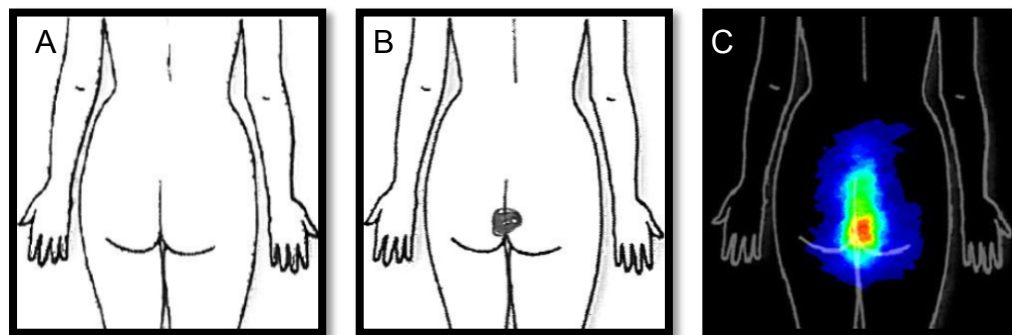


FIGURE 40 – EXAMPLE OF (A) EMPTY IMAGE, (B) SHADING OF THE AREA ASSOCIATED WITH THE “CALL TO STOOL” BY A HEALTHY VOLUNTEER, (C) COLOUR SCALED CUMMULATIVE IMAGE OF THE AREAS ASSOCIATED WITH THE “CALL TO STOOL” IN HEALTHY VOLUNTEERS AS A WHOLE

For all images, the total shaded area (in pixels) and the central X / Y pixel co-ordinates of the shaded area were obtained for both the anterior and posterior image. The anterior and posterior area were then summed to produce a numerical ‘total area in which sensation was experienced’ value.

13.2.3.2 Statistical analysis

Comparison of quality, location and strength of urge was compared between healthy volunteers and patients with constipation as well as between patients with RH, or with normal sensation (NS). Categorical statistical analysis (i.e. urge / lack of urge) was performed by a Fisher's exact test or chi-squared test where appropriate. For between groups analyses (i.e. area, X / Y co-ordinates), a t-test, Mann-Whitney U test, or one-way ANOVA, depending upon Gaussian distribution, were utilised where appropriate. A *P* value of <0.05 was considered statistically significant. Analyses were performed using a statistical analysis package (Prism 5.0 GraphPad Software, San Diego, CA, USA).

13.3 Results

13.3.1 Demographics

13.3.1.1 Healthy volunteers

Completed questionnaires were received from 44 healthy female volunteers (median age = 49, range 22 – 68). All healthy subjects denied any current gastrointestinal symptoms and had no past or current history of chronic gastrointestinal illness. In total 191 defaecatory attempts were analysed with a mean number of defaecation attempts per subject of 4.3.

13.3.1.2 Patients

Data was obtained from 157 female patients (median age = 52, range 17 - 82) with chronic constipation who had completed the viscerosensory questionnaire and undergone anorectal physiological investigations including evacuating proctography as defined in Chapter 10 as part of their clinical evaluation. One hundred and five patients had normal rectal sensation to balloon distension. Thirty-six patients were found to be hyposensitive and 15 had rectal hypersensitivity. Patients with rectal hypersensitivity were excluded due to their small numbers, leaving 141 patients with constipation with normal sensation or rectal hyposensitivity for comparison.

In total, 595 defaecatory attempts were assessed in these 141 patients, at an average of 4.2 defaecation attempts per patient. Patients with RH and patients with normal sensation described a similar number of attempts per patient (NS = 4.3 vs. RH = 4.1; $P = 0.47$).

13.3.2 Clinical findings

13.3.2.1 Stool consistency

(Figure 41)

Overall, both patients and healthy volunteers reported a median Bristol stool score of 4. However, patients described a greater spread across all stool consistencies than healthy individuals (overall 1 – 7; $P < 0.0001$) (Figure 41). Patients were more likely to describe abnormal stool

consistencies (Bristol 1 – 2, HV = 16% vs. CC = 26%; $P=0.006$ and Bristol 6 – 7, HV = 4% vs. CC = 18%; $P<0.0001$), whereas volunteers were more likely to describe normal consistency stools (Bristol 3 – 5. HV = 74% vs. CC = 48%; $P<0.0001$).

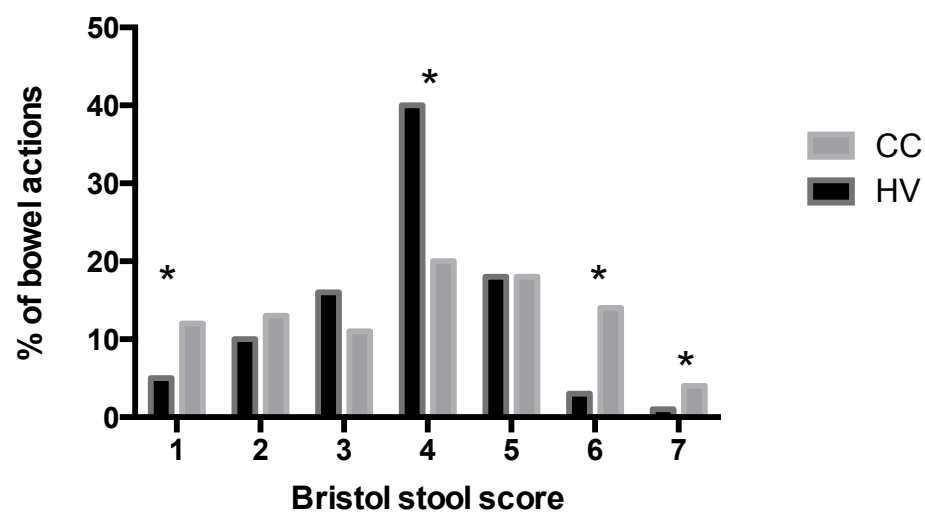


FIGURE 41 – REPORTED STOOL CONSISTENCY AS DETERMINE BY BRISTOL STOOL SCORE IN PATIENTS WITH CONSTIPATION AND HEALTHY INDIVIDUALS

* = $P < 0.05$.

Stool consistency did not appear to be influenced by sensory status (Bristol scale 1 – 7; $P=0.60$) (Figure 42).

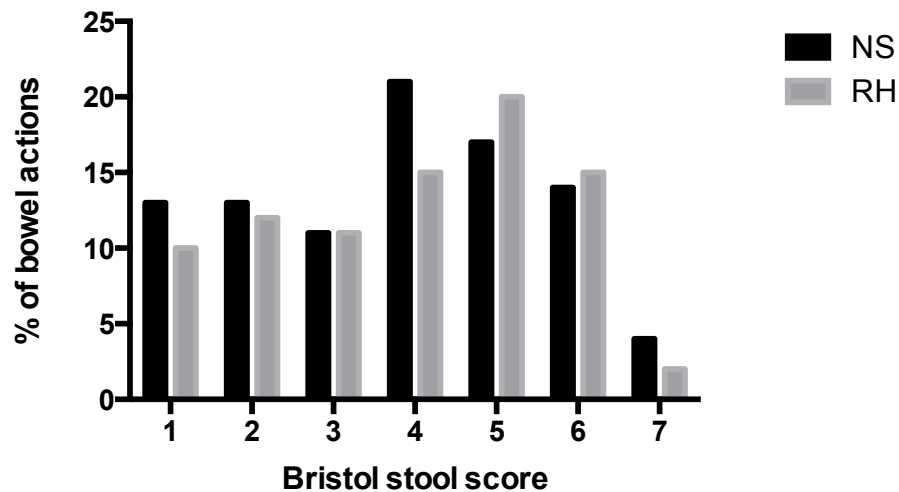


FIGURE 42 – BRISTOL STOOL SCORE IN CONSTIPATED PATIENTS STRATIFIED BY RECTAL SENSORY STATUS

(ALL VALUES = NON SIGNIFICANT).

13.3.2.2 Straining

Straining was uncommon in healthy volunteers, described on only 6% of occasions. By contrast, patients described significant straining on more than one third of occasions ($P<0.0001$). The presence of straining was not influenced by sensory status (NS = 38% vs. RH = 33%, $P=0.23$).

13.3.2.3 Defaecation success and completeness of evacuation

Healthy individuals described <1% of defaecation attempts as “unsuccessful” compared to patients who noted unsuccessful attempts to defaecate on 6% of occasions ($P=0.001$). Healthy volunteers also

recorded evacuation as being more complete than constipated patients with a significantly higher median VAS score (HV = 9.2 vs. CC = 4; $P < 0.0001$). Neither rate of unsuccessful defaecation (both NS & RH = 6%) or completeness of evacuation (median VAS score, NS = 3.8 vs. RH = 4.2, $P = 0.39$) was influenced by rectal sensory status.

13.3.2.4 Quality of the urge to defaecate

(Table 17)

Healthy volunteers used a median number of 2 descriptive terms when describing the urge to defaecate, most commonly reported as “pressure” (52%), followed by “fullness” (43%) and “heaviness” (19%). Less commonly, bloating (15%) and aching (11%) was also described. All other word triggers provided in the questionnaire were infrequently selected (on less than 10% of occasions).

Constipated patients differed significantly from healthy individuals in the manner in which they described the urge to defaecate. Firstly, patients used a greater number of descriptive terms overall (median = 3; $P < 0.0001$) and, secondly, whilst “pressure” was still the most common descriptive term (50%), patients recorded additional more varied descriptions.

TABLE 17 – DESCRIPTIVE TERMS REPORTED BY HEALTHY VOLUNTEERS AND PATIENTS WITH CONSTIPATION WHEN DESCRIBING THE URGE TO DEFAECATE.

Descriptive terms used	Healthy volunteers	Chronic constipation	P - value
Pressure	52%	50%	0.6
Fullness	43%	31%	0.005
Heaviness	19%	20%	0.8
Bloating	15%	31%	<0.0001
Aching	11%	20%	0.003
Cramping	8%	16%	0.005
Squeezing	7%	6%	0.6
Tingling	5%	1%	<0.0001
Spasm	5%	9%	0.08
Butterflies / gurgling	4%	8%	0.03
Throbbing	3%	2%	0.4
Colicky / griping	2%	10%	<0.0001
Irritation	2%	5%	0.055
Stabbing	1%	6%	0.005
Nausea	0%	10%	<0.0001
I can't describe	3%	3%	0.81
Other	3%	11%	0.0005

Overall, healthy volunteers were much more likely to utilise “typical descriptors” (pressure, heaviness or fullness) when describing the urge to

defaecate than those with constipation (HV = 78% vs. CC = 66%, $P < 0.002$). Patients by contrast, were more likely to use free text descriptive terms, rather than those provided by the questionnaire (HV = 3% vs. CC = 11%, $P = 0.0005$) (Table 17). These included the urge to urinate or pass wind as a stimulus for defaecation; however, generalised systemic symptoms such as sweats, shakes or generalised pain were also commonly recorded (19%). Such stimuli were never reported by healthy individuals.

When patients were stratified by rectal sensory status (NS vs. RH) (Table 18) patients with RH were less likely to use “typical descriptors” (NS = 69% vs. RH = 55%, $P = 0.003$). Patients with RH were also more likely to use free text descriptors ($P = 0.03$).

TABLE 18 – DESCRIPTIVE TERMS REPORTED BY PATIENTS WITH CONSTIPATION WHEN DESCRIBING THE URGE TO DEFAECATE STRATIFIED BY SENSORY STATUS.

Descriptive terms used	NS	RH	P - value
Pressure	52%	42%	0.056
Fullness	34%	23%	0.01
Heaviness	24%	9%	<0.0001
Bloating	31%	33%	0.6
Aching	20%	21%	0.7
Cramping	16%	15%	1
Squeezing	6%	5%	0.8

Descriptive terms used	NS	RH	P - value
Tingling	1%	0%	0.6
Spasm	8%	10%	0.5
Butterflies / gurgling	9%	6%	0.3
Throbbing	2%	1%	0.7
Colicky / griping	10%	8%	0.4
Irritation	5%	5%	0.5
Stabbing	6%	5%	0.7
Nausea	8%	13%	0.1
I can't describe	4%	1%	0.058
Other	10%	16%	0.03

13.3.2.5 Strength of the urge to defaecate

Healthy volunteers reported a median urge VAS intensity of 6.9. Constipated patients overall, had a reduced intensity of the urge to defaecate (VAS = 5.9; $P=0.0004$) vs HV. There was a no difference in intensity of urge in patients with RH compared with NS (NS = 5.9, RH = 5.8; $P=NS$).

13.3.2.6 Absence of the urge to defaecate

In healthy volunteers, defaecation occurred without a clear sensory urge on only 10 (5%) of occasions, seen in eight individuals (with two individuals describing it on more than one occasion), often following

urination. By contrast, forty-seven (33%) constipated patients described loss of the urge to defaecate, with 23 (16%) patients describing it on more than one occasion ($P = 0.04$). Overall, patients defaecated without a clear urge to do so on 16% of occasions (HV vs. CC; $P < 0.0001$). Patients with RH described an absence of the urge to defaecate more frequently than those with normal rectal sensation. (NS = 14% vs. RH = 21%; $P = 0.049$).

13.3.2.7 Location of the urge to defaecate

13.3.2.7.1 Overall location

In general, healthy volunteers (Figure 43) described the location of “urge” in one of two places. Most commonly, sensation was noted in the posterior perianal or rectal region, with healthy subjects describing an isolated posterior sensation of 41% of occasions. On 22% of defaecatory efforts, healthy individuals described an anterior sensation (most often suprapubic) in isolation, with 31% of defaecatory attempts described as having both anterior and posterior sensations.

Constipated patients (Figure 43) most commonly reported *both* an anterior and posterior sensation as the urge to defaecate (37%). Patients, in comparison to healthy individuals, were significantly less likely to describe an isolated posterior sensation (CC = 30% $P = 0.003$ vs. HV). Patients were also less likely to describe an anterior sensation in isolation although this did not reach statistical significance.

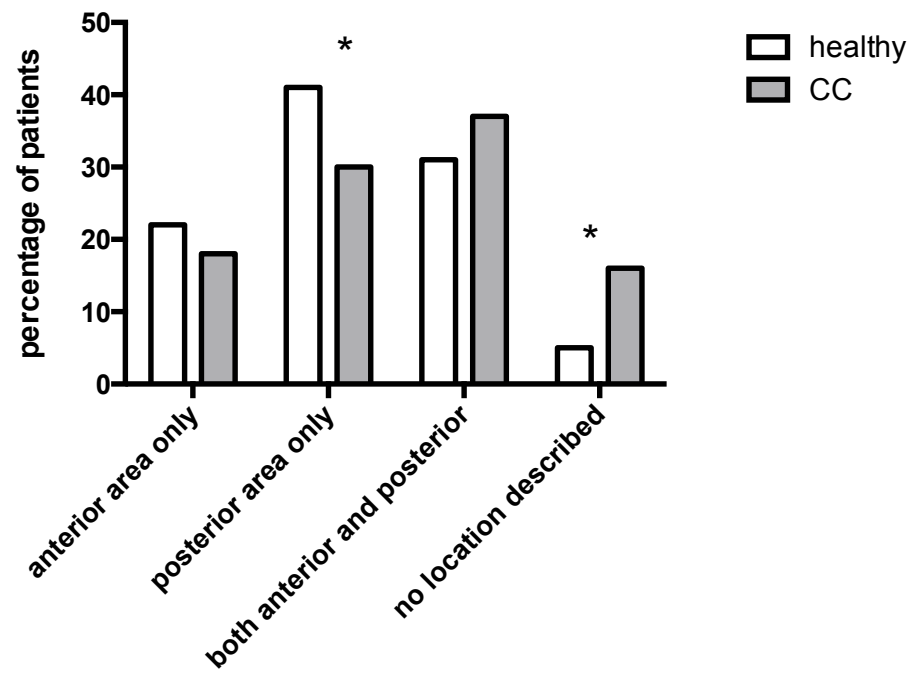


FIGURE 43 – OVERALL LOCATION OF THE SENSATION DESCRIBED AS THE URGE TO DEFAECATE BY HEALTHY INDIVIDUALS (WHITE) AND PATIENTS WITH CONSTIPATION (GREY).

* P < 0.05.

Both patients with RH and NS described the urge to defaecate in similar areas although patients with RH were unable to localise sensation more often than those with normal sensation (Figure 44) (NS = 14% vs. RH = 21%; $P=0.049$).

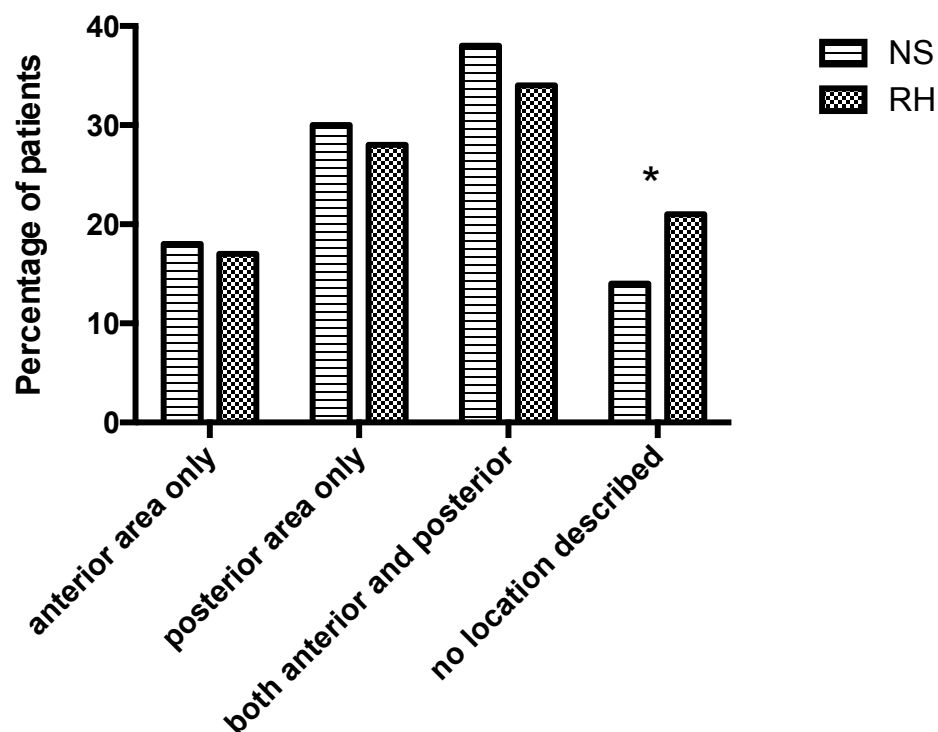


FIGURE 44 – OVERALL LOCATION OF THE SENSATION ASSOCIATED WITH THE URGE TO DEFAECATE IN CONSTIPATED PATIENTS STRATIFIED BY SENSORY STATUS.

($P = 0.049$)

13.3.2.7.2 Central point of sensation

The mean central X / Y co-ordinates of the shaded area, both posteriorly and anteriorly (Figure 45) were not significantly different between healthy volunteers and constipated patients, although the central location (X / Y

co-ordinates) of sensation was spread more widely in patients than healthy individuals (coefficient of variance anteriorly for X point HV = 8.5% vs. CC = 10.7% and for Y point 14.9% vs. 17.9%, respectively; coefficient of variance posteriorly for X point HV = 4.4% vs. CC = 6.0% and for Y point 15.6% vs. 16.9% respectively) although this was not statistically significant.

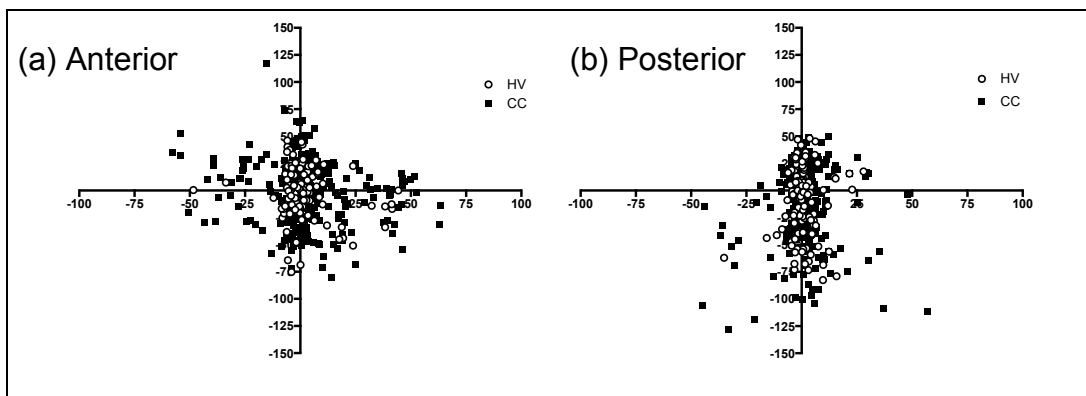


FIGURE 45 – Z-SCORE (USING HEALTHY MEDIAN) SCATTER PLOT OF THE X AND Y CO-ORDINATES OF THE CENTRE OF THE AREA ASSOCIATED THE URGE TO DEFAECATE ANTERIORLY (A) AND POSTERIORLY (B) IN HEALTH AND PATIENTS WITH CONSTIPATION.

HEALTHY INDIVIDUALS ARE SHOWN AS WHITE CIRCLE AND CONSTIPATED PATIENTS BLACK SQUARES.

The X / Y co-ordinates of the centre both anteriorly and posteriorly were similar between sensory subgroups (Figure 46) (coefficient of variance front X point, NS = 11.7% vs. RH = 10.6% and Y point 17.3% vs. 17.6% respectively, coefficient of variance back X point, NS = 6.5% vs. RH = 5.9% and Y point 16.7% vs. 17.4% respectively; P=NS).

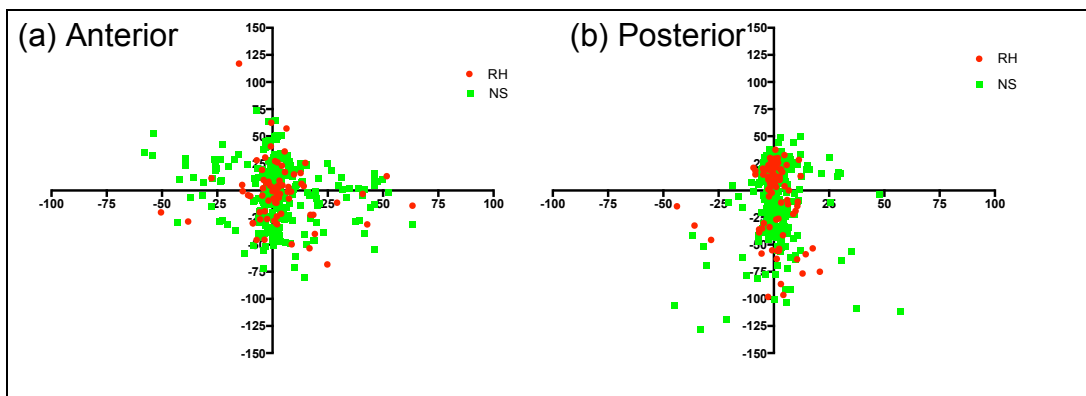


FIGURE 46 – Z-SCORE (USING HEALTHY MEDIAN) SCATTERPLOT. X AND Y CO-ORDINATES OF THE CENTRE OF THE AREA ASSOCIATED THE URGE TO DEFAECATE ANTERIORLY (A) AND POSTERIORLY (B) IN PATIENTS WITH CONSTIPATION STRATIFIED BY RECTAL SENSORY STATUS DETERMINED BY LATEX BALLOON DISTENSION

(GREEN = NS, RED = RH).

13.3.2.7.3 Magnitude of area shaded

When size of the area of sensation plotted was compared, patients and healthy individuals described a similar sized area of sensation posteriorly (pixel area = median [IQR] HV = 1021 [526 – 1604] vs. CC = 1021 [594 – 1953]; P = 0.16). However, patients described a significantly larger area of sensation anteriorly (HV = 1017 [603 – 1677] vs. CC = 1490 [810 – 3376]; P < 0.0001). Thus, overall, patients reported a larger total area of

sensation (pixel area = median [IQR] HV = 1303 [704 – 2160] vs. CC = 1773 [819 – 3521]; $P < 0.0001$).

This is represented below in the cumulative spatial map created from reported location of sensation from all healthy volunteers and patients with constipation, highlighting visually the differing magnitude and location of sensation noted by HV and constipated patients (Figure 47).

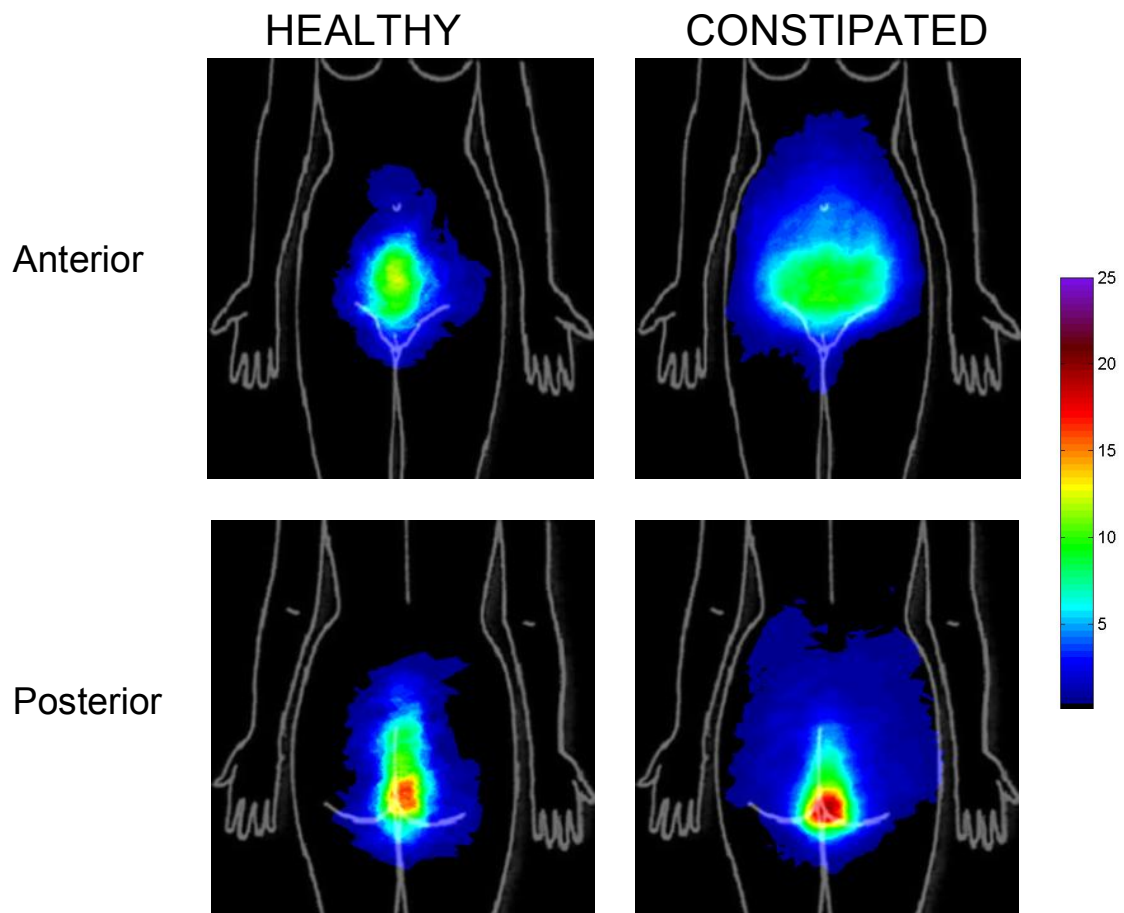


FIGURE 47 – ACCUMULATED SENSORY MAP OF THE AREA IN WHICH SENSATION IS EXPERIENCED DURING THE URGE TO DEFAECATE IN PATIENTS AND HEALTHY VOLUNTEERS

SCALE = PERCENTAGE OF SUBJECTS.

When patients who described urge were stratified by sensory status, it was seen that patients with RH described a greater area of anterior sensation than those with normal sensation (median [IQR], NS = 1326 [758 – 2738] vs. RH = 2659 [1218 – 4825]; $P < 0.0001$) and greater area overall (NS = 1652 [803 – 3109] vs. RH = 2454 [869 – 5757]; $P = 0.006$). However, there was no difference in the area of posterior sensation (median [IQR], NS = 1013 [569 – 1773] vs. RH = 1062 [683 – 2235]; $P = 0.2$) (Figure 48).

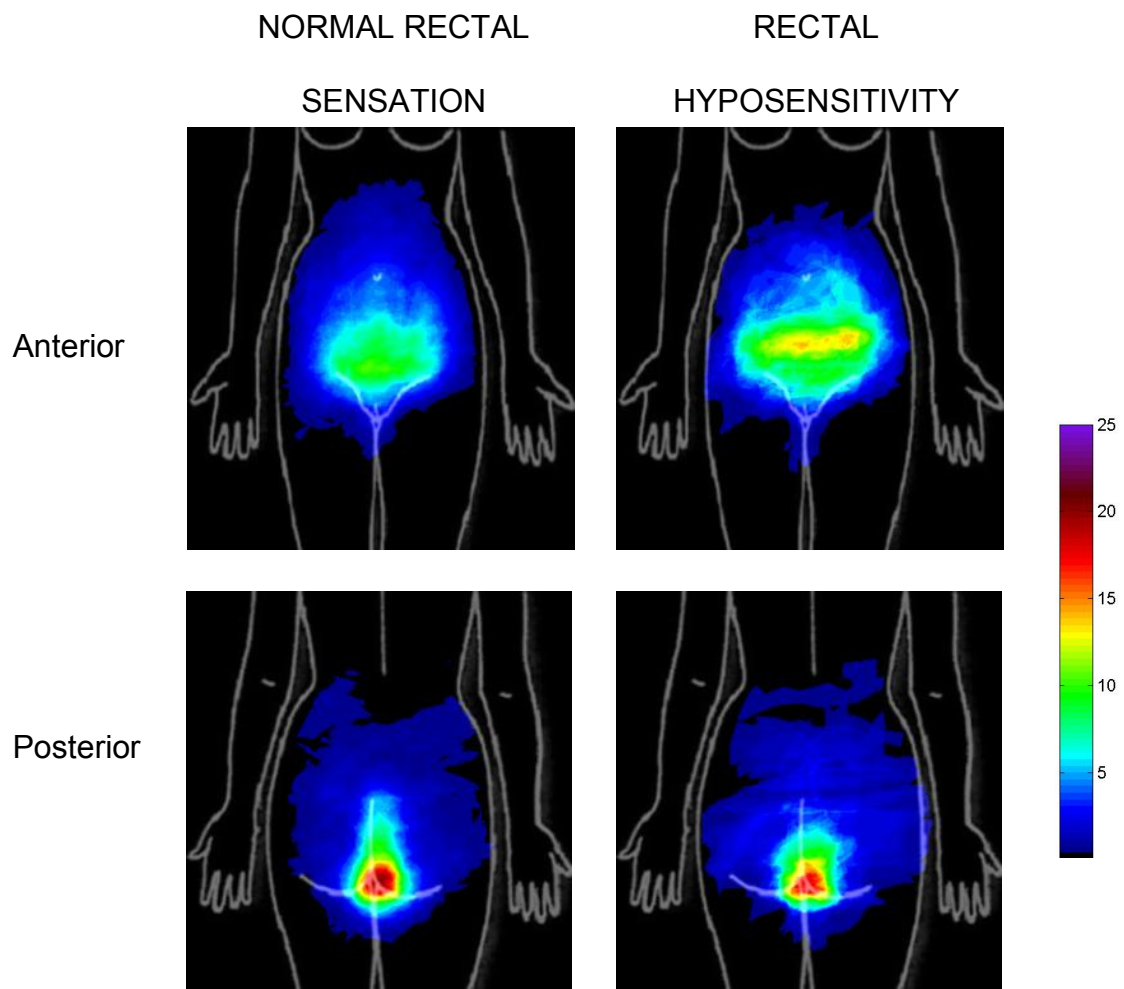


FIGURE 48 – ACCUMULATED SENSORY MAP OF THE AREA IN WHICH SENSATION IS EXPERIENCE DURING THE URGE TO DEFAECATE IN CONSTIPATED PATIENTS STRATIFIED BY RECTAL SENSORY STATUS TO LATEX BALLOON DISTENSION.

13.3.3 Comparison of “normal” vs. abnormal area of sensation

While it is clear that patients as a group have a more diffuse sensation associated with the urge to defaecate than healthy individuals, there is considerable overlap. This suggests that abnormal viscerosensory sensation may only exist in a proportion of patients with constipation; perhaps defining a group with true afferent nerve dysfunction.

To determine this a post-hoc analysis was performed with patients subgrouped into normal viscerosensory referral (defined as an area within the 5th and 95th centiles of healthy volunteer “total area of sensation” data) and abnormal (falling outside these values).

Replicating the structure of the ROME III criteria (Longstreth *et al.*, 2006) which requires patients to have symptoms on at least 25% of occasions, individual patients were defined as having abnormal perception of the urge to defaecate if the size of area in which sensation was experienced was abnormal on more than 25% of defaecatory attempts. This classification defined 34 subjects (25%) with constipation as abnormal ($C_{(abN)}$) and 107 subjects (75%) as normal ($C_{(N)}$). Anorectal physiology results and clinical history / risk factors were compared between subgroups.

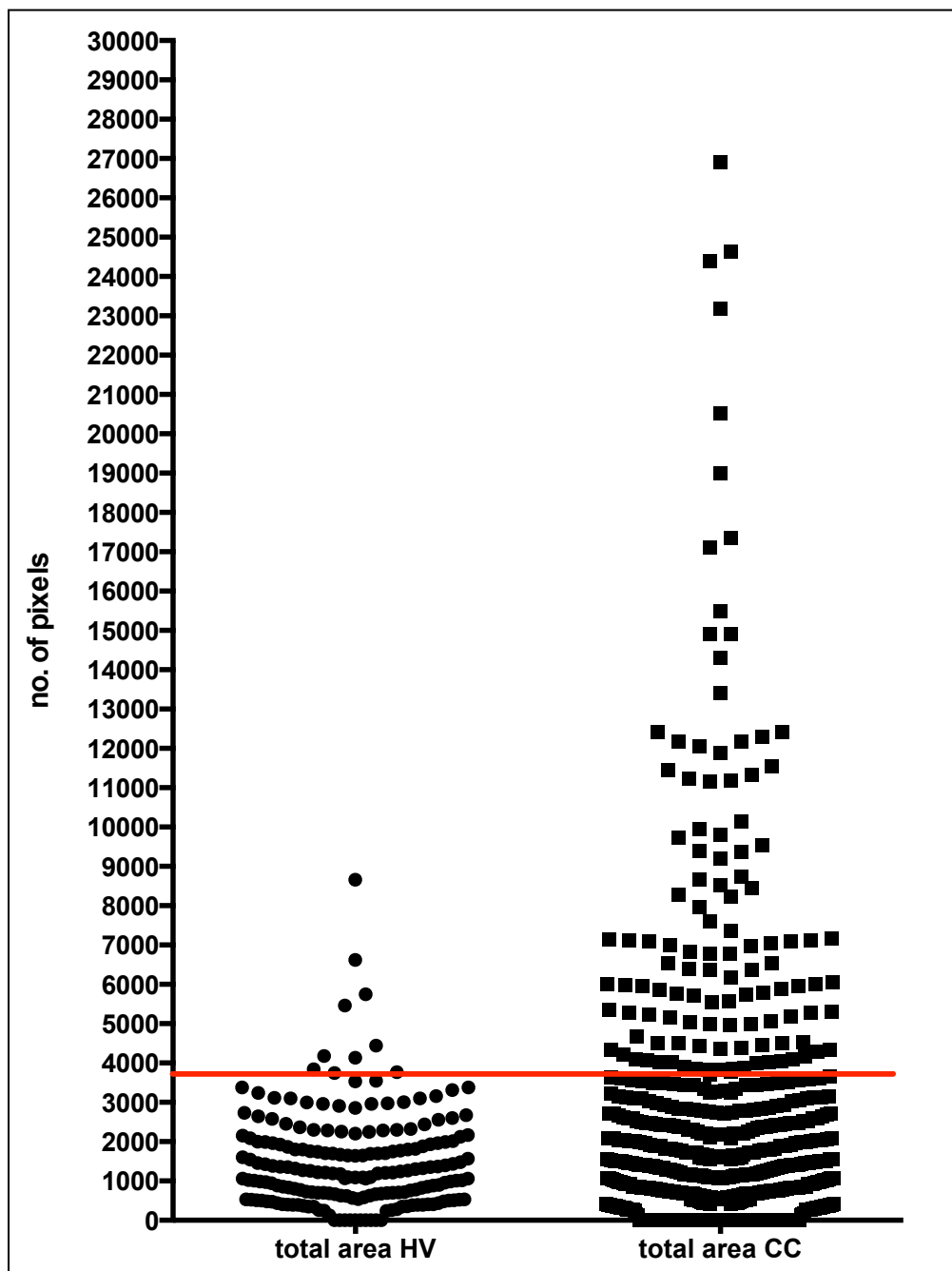


FIGURE 49 – SCATTER PLOT OF TOTAL AREA OF SENSATION IN HEALTHY VOLUNTEERS AND CONSTIPATED PATIENTS.

THE RED LINE DEFINES UPPER LIMIT OF NORMAL, EQUATING WITH THE 95TH CENTILE OF THE HEALTHY VOLUNTEER DATA. THERE IS NO LOWER LIMIT OF NORMAL, AS THE HEALTHY VOLUNTEER DATA 5TH PERCENTILE WAS ZERO.

There was only one physiological abnormality associated with abnormal sensation of the urge to defaecate. Patients with abnormal sensation were more likely to have RH than those with a normal sensation ($C_{(N)} = 21\%$ vs. $C_{(abN)} = 41\%$; $P = 0.02$). Rates of evacuatory dysfunction on proctography, presence of a clinically significant rectocele, presence of clinically significant intussusception or features of dyssynergic defaecation were similar between groups (Figure 50).

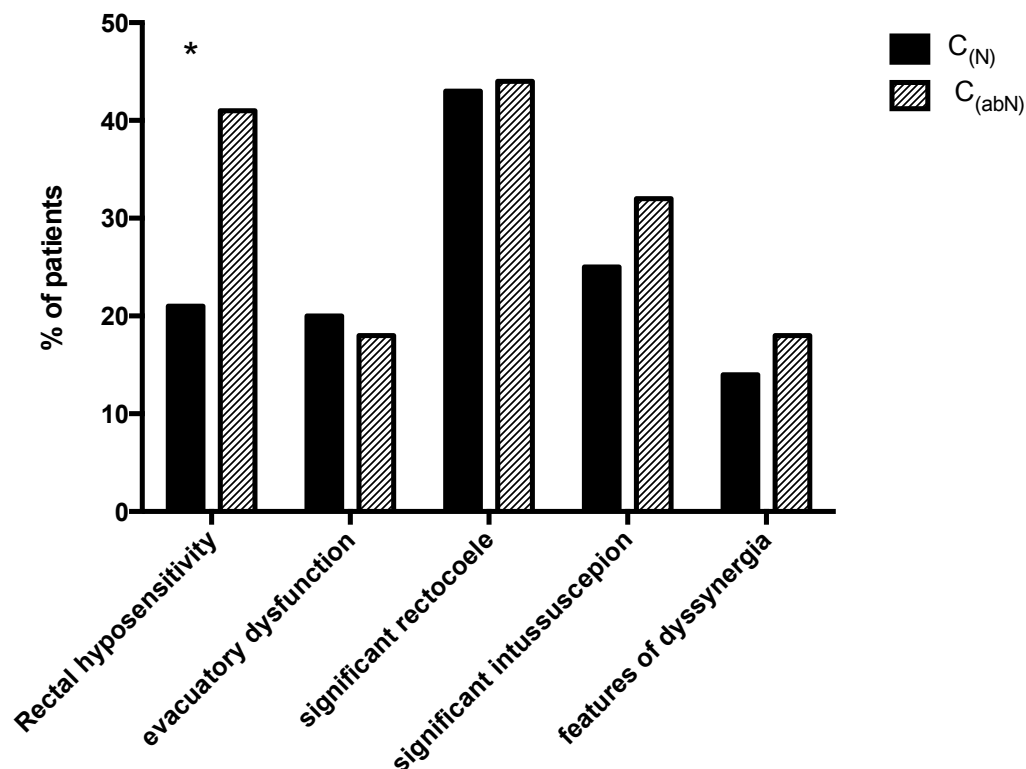


FIGURE 50 – COMPARISON OF RESULTS OF ANORECTAL PHYSIOLOGICAL ASSESSMENT IN PATIENTS WITH CONSTIPATION AND NORMAL AREA OF SENSATION ($C_{(N)}$) WITH THOSE WITH CONSTIPATION AND AN ABNORMAL AREA OF SENSATION ($C_{(ABN)}$).

* $P=0.02$.

Patients with an abnormal area of sensation were significantly less likely to describe a prior history of obstetric injury than those with a normal area of sensation. Otherwise, there was no difference in the incidence of any other risk factors between groups (Figure 51).

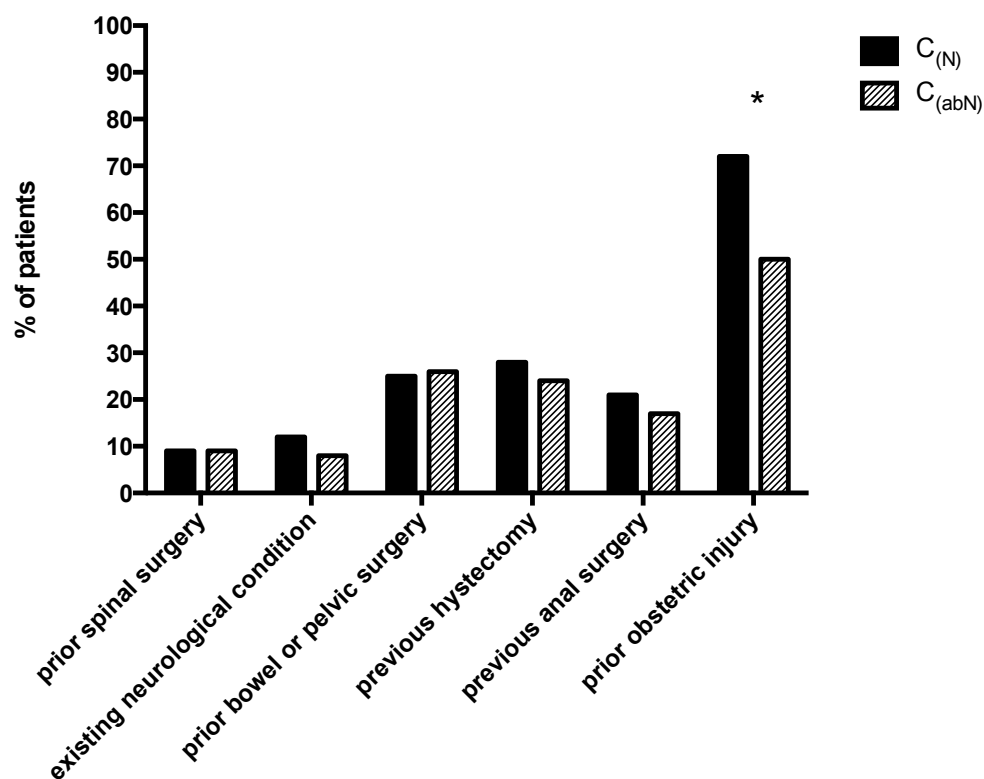


FIGURE 51 – COMPARISON OF RISK FACTORS FOR HINDGUT DYSFUNCTION BETWEEN PATIENTS WITH CONSTIPATION AND NORMAL AREA OF SENSATION ($C_{(N)}$) AND PATIENTS WITH CONSTIPATION AND ABNORMAL AREA OF SENSATION ($C_{(abN)}$).

* $P=0.02$.

13.4 Discussion

This study has systematically explored the role of perception of the urge to defaecate in the clinical presentation of constipation. The results support the notion that impairment of sensory function is associated with hindgut

dysfunction. For the first time, this study has shown objectively that patients with constipation have a significant alteration in the call to stool compared to healthy individuals with clear differences regarding location, size, quality and strength of urge between patients and healthy individuals. Furthermore, although traditional symptoms were similar between patients with either normal or blunted rectal sensation (rectal hyposensitivity), a proportion of individual patients with constipation, particularly those with RH clearly had clinically identifiable alterations on detailed questioning. This suggests that current clinical history taking techniques, focussed on stool consistency and frequency alone, may be inadequate when assessing patients for the presence of abnormal gut function.

Results in healthy individuals found that normal defaecation generally involves a well-defined perianal or rectal sensation, most often described as a sense of “fullness”, “pressure” or “heaviness”. By contrast, constipated patients describe a weaker, more diffuse abdominal and perianal sensation, and are more likely to use multiple varied descriptive terms to describe the urge to defaecate. One hypothesis is that constipated patients (particularly those with known impairment of rectal sensation to distension [RH], in whom the call to stool was most aberrant) are inattentive to normal signals from the rectum responsible for triggering the urge to defaecate, instead only responding to colonic or anal sensations. This would account for the more diffuse area of sensation seen, the increased frequency of anterior symptoms as well as the

increased frequency of descriptors such as colic, nausea, bloating and aching; all symptoms that are generally associated with intestinal rather than rectal sensations (Goligher and Hughes, 1951, Ford *et al.*, 1995). This may also explain why the central area of sensation did not differ between groups, as patients would still experience normal cues for defaecation, albeit without recognising their importance and thus including them in their overall description of the call to stool, even though the sensation itself is insufficient to trigger defaecation. Such patients may subconsciously defer defaecation, responding only when secondary cues (i.e. abdominal pain as a result of sigmoid distension) occur, resulting in a greater area in which sensation is experienced and accounting for the common involvement of both anterior and posterior areas. This hypothesis is supported by a recent paediatric study in patients with constipation which found that in subjects who denied an urge to defaecate, colonic propagating complexes, normally seen prior to evacuation, were accompanied by retentive posturing and grimacing indicating misinterpretation of defaecatory urge as pain. When it was explained to the individual that the sensation they were experiencing was in fact “urge”, all subjects were able to defaecate normally on subsequent occasions (Firestone Baum *et al.*, 2013). This may also explain why, although there was a clear difference between defaecatory urge between healthy individuals and patients, there are less dramatic differences in the quality of defaecatory urge between sensory groups. Long standing inattention to defaecatory urge in patients with constipation may lead to a spectrum of

sensory dysfunction, raising the possibility that RH may be the end result of progressive desensitisation of the rectum following chronic inattention to normal sensory defaecatory signals. This is consistent with the finding that subjects with RH have more aberrant defaecatory urge (and increased frequency of total absence of defaecatory urge) than those with NS.

When patients were considered as individuals and divided into those with a normal area of sensation associated with the urge to defaecate (“normal call to stool”) or abnormal area of sensation (“abnormal call to stool”), the only discernible physiological abnormality associated with an “abnormal call to stool” was the presence of RH. While twice as many individuals with RH described an abnormal “call to stool” compared with those with NS, the majority of patients (almost 60%) with RH still reported normal sensory patterns. This suggests that only a subgroup of individuals with RH diagnosed by balloon distension have clinically significant abnormal afferent function. These findings fit well with previous physiological studies (Gladman *et al.*, 2009) that have shown that up to 50% of patients diagnosed with RH via latex balloon distension have primary biomechanical abnormalities of the rectal wall with normal mucosal electrical sensitivity. In such patients, although a greater bolus of stool would be required to trigger defaecation due to the increased distensibility of the rectum, the sensory apparatus itself appears to be intact and thus a normal sensory experience of the call to stool would be expected. Collagen abnormalities such as seen in the joint hypermobility syndrome

have been postulated to be the common aetiological link in such a scenario (Zarate *et al.*, 2010). Benign joint hypermobility (BJHM), as diagnosed by the Beighton score (Fikree *et al.*, 2013) which is associated with a multisystem disorder leading to chronic pain, dysautonomia and gastrointestinal dysmotility (Hakim and Grahame, 2003), is found in approximately 40% of the population (Fikree *et al.*, 2013) but is more commonly seen in patients with functional gastrointestinal disorders, particularly rectal evacuatory dysfunction (Mohammed *et al.*, 2010, Zarate *et al.*, 2010). While rectal compliance has not been formally tested in such patients, prior studies have suggested that higher rates of BJHM in patients with functional gastrointestinal disorders may be secondary to altered gut viscoelastic properties (Zarate *et al.*, 2010). Certainly rectal hypercompliance may result in altered sensory response to rectal distension despite intact afferent function (as discussed in chapter 10) although it is noted that rectal hyposensitivity as determined by balloon distension is seen equally in patients with or without joint hypermobility (Mohammed *et al.*, 2010). A future study examining the relationship between BJHM, altered visceral sensory function / compliance and defaecatory urge would be worthwhile.

Interestingly, patients with an abnormal call to stool were less likely to report obstetric injury. This raises the possibility that such constipated patients may have a primary afferent neuropathic process, whether this be receptor, neuronal or cortical (such as resulting from progressive

inattention to defaecatory urge with eventual loss of urge) (Klauser *et al.*, 1990), underlying their symptoms, rather than an acquired injury such as from childbirth (Snooks *et al.*, 1984, Snooks *et al.*, 1990). It would be interesting to examine whether patients with an abnormal call to stool have a longer duration of symptoms (i.e. present from childhood), which would support this hypothesis. A study powered to this end point would be worth addressing.

It also remains to be seen, as noted in patients with RH (Chapter 11), if patients with alteration of the call to stool also have a more severe clinical phenotype overall. Whilst a number of studies have examined the association of sensory dysfunction with hindgut disorders (De Medici *et al.*, 1989, Mertz *et al.*, 1995, Gosselink and Schouten, 2001, Gladman *et al.*, 2003a, Sloots and Felt-Bersma, 2003, Chan *et al.*, 2005a, Wijffels *et al.*, 2011, Lee *et al.*, 2013), few have focussed on its clinical impact. Of those, most report only gross changes (i.e. absence or presence) of the urge to defaecate. Harraf *et al.* (Harraf *et al.*, 1998), examined patients with constipation-predominant irritable bowel syndrome, and found that RH was associated with “no urge” constipation. They hypothesised, as there was no alteration in rectal compliance between groups, that hyposensitivity or inattentiveness to normal rectal sensation was secondary to primary rectal afferent dysfunction. This was also the premise of Gladman *et al.* (Gladman *et al.*, 2003a, Gladman *et al.*, 2005), who found that many patients with rectal hyposensitivity and constipation

had entirely normal rectal dimensions and compliance, suggesting primary afferent pathology may contribute to their symptoms.

In contrast to RH, rectal hypersensitivity has been more extensively studied. In the IBS literature, where the bulk of research has been performed, rectal hypersensitivity is associated with a greater viscerosensory referral area and amplification of normal gut sensations to the extent that they are perceived as pathological (Mertz, 2003). Chan *et al.* (Chan *et al.*, 2005c) also examined the clinical impact of rectal hypersensitivity in hindgut dysfunction, albeit in patients with urge faecal incontinence. They found that patients with rectal hypersensitivity had increased stool frequency, increased use of pads and a greater impact on lifestyle than patients with normal sensation despite both groups having a similar number of incontinence episodes. Both these studies proposed hypervigilance (and / or sensory amplification) as a likely mechanism for symptom generation in patients with rectal hypersensitivity.

Caution should, however, be taken when interpreting the results of this study. Firstly, formal validation of the viscerosensory questionnaire in patients has not yet been completed. This is predominantly because there is no gold standard with which to compare the questionnaire. Although the questionnaire is sensitive enough to detect differences between groups, it is not clear to what degree this is a factor of “within patient variation” versus “between subject variation”. While repeated measures were

recorded for each subject, they were done so within a five day period and hence are open to reporting bias (patients may be influenced by the results of the previous days recording). Formal validation within a structured clinical study with repeated measures spaced appropriately apart should be undertaken. Unavoidable reporting bias may also have influenced the findings as constipated patients may, as a result of chronic symptoms, be more focused on bowel sensations than healthy individuals.

The use of multiple comparisons within the study also limits the strength with which conclusions may be drawn. The large sample size does allow for statistical significance to be reached where perhaps clinical significance is less clear. One way of dealing with this is to accept a more stringent definition of significance (i.e. $P = 0.002$ calculated using a conservative Bonferroni correction for the multiple comparisons used within this study). Using this definition, patients with constipation still had statistically significantly difference in the percentage of patients without defaecatory urge, size of the area associated with defaecatory urge, completeness of defaecation, number of descriptive terms utilised to describe urge and a number of specific descriptors (i.e. pressure, fullness or heaviness, bloating etc.), although the difference seen between those with RH and NS were less clear. Size of the area associated with the urge to defaecate remained the main discriminator between subgroups. Overall, given the statistical signals detected were clinically appropriate and theoretically valid, it is felt that the findings are very likely to be true and

pathophysiological relevant, however the clinical significance of the demonstrated increased risk would require further study given the small odd ratios.

This study is also limited in that daily laxative use was not included as part of the questionnaire. More frequent laxative use in patients could result in the increased area of sensation described or indeed the abnormal / different descriptors seen. However, despite these limitations, this study has value. It is the first to show a clear clinical impact of sensory dysfunction on clinical presentation. It also suggests that traditional methods of assessing symptoms of constipation (stool form, frequency, straining) are not adequate, with this study identifying a subgroup of patients with likely sensory abnormality that would otherwise be overlooked. Comprehensive assessment of constipated patients should thus include focussed questioning to determine whether an abnormality of the call to stool exists. The use of a sensory questionnaire, as employed within this study, has potential important clinical implications. As a bare minimum, targeted questions addressing presence or absence of urge, location of urge and quality of urge should be employed. Constipation, like breathlessness, is a symptom. As seen with breathlessness, which has multiple underlying causes all with very varied treatment paradigms (cardiac failure, infection, embolism etc.), constipation is also likely to result from multiple pathogenic mechanisms, many of which are, as yet, undefined. Effective treatment of constipation requires accurate

identification of such pathological subtypes, either via clinical or physiological assessment, so that targeted therapy can be offered to the individual sufferer. The viscerosensory questionnaire utilised in this study, is thus a “low tech” tool with significant potential implications for clinical care. Formal validation should be undertaken, with repeatability studies performed. Further research should be performed to determine if stratification of patients based on the results of the questionnaire predicts response to treatment, or alternatively if effective treatment in abnormal patients is associated with appropriate normalisation of sensory descriptions as defined by the questionnaire.

13.5 Conclusions

This study is the first to confirm aberrant perception of the urge to defaecate in patients with constipation, most notably those with RH. Such patients had alteration of the location and area of sensation as well as the quality and strength of sensation. Experiencing a defaecatory urge is fundamental to normal defaecation; alteration of this urge in constipated patients is likely a result of primary rectal afferent pathway dysfunction, or alternatively, cortical inattention due to progressive desensitisation.

Patients with RH were more likely to describe loss of the urge to defaecate and more frequently used atypical descriptive terms when describing the quality of sensation. In patients with RH, the call to stool was significantly

more aberrant in regards to size and location of sensation than in those with normal rectal sensation, further supporting the concept that rectal sensory mechanisms have an important role in normal defaecation and the generation of defaecatory urge.

Finally, when patients were considered as individuals and stratified into groups based on the presence of a normal or abnormal call to stool, the only physiological abnormality associated with abnormal patterns of sensation was sensory dysfunction. Whether therapies targeted at sensory dysfunction result in improvement of the parameters of defaecatory urge is yet to be confidently established. However, rectal sensory dysfunction should be considered an important therapeutic target in patients with functional constipation and further research is warranted to this end.

14 ASSESSMENT OF AFFERENT NEURONAL PATHWAYS IN HEALTH AND PATIENTS WITH CONSTIPATION ASSOCIATED WITH RECTAL HYPOSENSITIVITY USING RECTAL EVOKED POTENTIALS AND INVERSE MODELLING

14.1 Introduction

Traditionally, the principal mechanisms underlying chronic constipation have been considered as colonic dysmotility and rectal evacuatory dysfunction, though considerable overlap is recognised (Cook *et al.*, 2009). However as shown in this thesis, integrity of sensory function is also fundamental to the process of defaecation (Lunniss *et al.*, 2009, Gladman *et al.*, 2003b). Rectal hyposensitivity is found in almost one-quarter of adults (Gladman *et al.*, 2003a) and two-thirds of children with chronic constipation (Meunier *et al.*, 1979), and is often the only discernible physiological abnormality on comprehensive testing (Gladman *et al.*, 2003a). As shown in earlier chapters, patients with rectal sensory dysfunction have alteration in the normal urge to defaecate with a proportion reporting complete absence of urge. Furthermore, it is clear that the presence of rectal hyposensitivity is associated with increased symptom frequency and overall severity of hindgut dysfunction, suggesting sensory impairment is an important mechanism for symptom generation.

Complete understanding of the mechanisms involved in the development of RH is currently lacking. Though RH was first recorded in patients with spinal transection / trauma (Sun *et al.*, 1990a), suggesting likely neuronal dysfunction as the underlying mechanism, it is also frequently seen in patients without overt neurological abnormalities. Previous work (Gladman *et al.*, 2005) suggests that RH may be due either to the impairment of rectal afferent function, the presence of altered rectal wall biomechanics (e.g. increased capacity or compliance) or a combination of both. However, direct assessment of the neuronal pathways in patients with RH has not yet been undertaken. As a result, in those with presumed afferent dysfunction without clinical explanation, the level at which pathology occurs (i.e. receptor / peripheral nerve / spinal pathways / central processing) is unknown.

By using somatic and visceral evoked potentials, and modelling of spatiotemporal processing of cortical information (described in more detail in Chapter 10), this study aims to confirm that in patients with constipation allied to blunted rectal perception (RH), the impairment of sensory function is secondary to an alteration in peripheral / spinal afferent neuronal function or central processing.

14.2 Methods

14.2.1 Subjects

The study was performed in conjunction with Aalborg University Denmark. Health volunteers were recruited both from Denmark and London.

14.2.1.1 Healthy volunteers

Thirteen healthy volunteers (nine female, median age 35, range 20 – 62) were recruited via advertisement. Subjects were excluded if there was any history of gastrointestinal (GI) disease, symptoms of GI dysfunction at the time of the study, or if they were taking medications known to affect GI function. One healthy volunteer was taking ramipril for hypertension with the remainder not taking any medications.

14.2.1.2 Patients

Seventeen patients with constipation and RH (all female, median age 46, range 20 – 62) were recruited from those who had previously undergone anorectal physiological investigation during their clinical diagnostic workup within the GI Physiology Unit. As part of this clinical examination, rectal sensory testing to simple balloon distension was performed and, to ensure a robust sample, RH was defined as elevation of two or more sensory thresholds above the normal ranges. All patients reported symptoms of chronic constipation, and fulfilled criteria for functional constipation (Thompson *et al.*, 1999). Patients who met the exclusion criteria as

defined in Chapter 10 were excluded. Patients were allowed to continue their standard laxatives. Two patients were taking oral bisacodyl, two senna, two polyethylene glycol, two glycerine suppositories, one flaxseed, one weekly sodium picosulfate / magnesium citrate and one patient was taking prucalopride and domperidone. One patient was taking fluoxetine as an antidepressant.

All healthy volunteers underwent rectal sensory function testing (as above), and did not proceed with the experiment if the results fell outside the normal range.

14.2.2 Experimental protocol

GI symptoms were assessed via practitioner-directed history, validated comprehensive bowel symptom questionnaire (Mohammed *et al.*, 2010), and Cleveland Clinic constipation score (Agachan *et al.*, 1996a) as described in Chapter 10. All subjects underwent a full neurological examination to exclude overt neurological disease. Digital rectal examination was performed to ensure an empty rectum and if significant stool was present, a warm 120 ml tap water enema was administered to aid rectal emptying. Rectal sensation to electrical stimulation was determined using a previously validated stimulation device (Brock *et al.*, 2008) (GMC ApS, Hornslet, Denmark) containing two stainless steel electrodes mounted at the tip, with an inter-electrode distance of 2 mm, connected to a computer-controlled constant-current stimulator (IES 230;

JNI Biomedical ApS, Klarup, Denmark). The subject was positioned in the left lateral position and the probe was advanced through the anus with the tip placed 10 cm from the anal verge and was secured to the buttock using adhesive tape to avoid movement. An upper safety limit of 80 mA was set.

Subjects were instructed to report: “first sensation”, equating with the point at which a definite sensation was experienced; “pain threshold”, the intensity at which the stimulus became uncomfortable; and “maximally tolerated sensation”, the intensity at which the stimulus was unable to be tolerated and the patient requested to stop.

14.2.2.1 Evoked potentials

Electroencephalograph (EEG) signals were recorded from 64 electrodes using the extended 10-20 system montage (Quick-Cap International, Neuroscan, El Paso, TX, USA). The cap was placed in a standardised position, with the centre of the anterior border 4 cm above the nasium. Electro-conductive gel (ECI Electro Gel, Electro Cap international) was applied to each electrode ensuring good contact between electrodes and scalp. Inter-electrode impedances were monitored and kept below 10 k Ω at all sites. Recordings were obtained in a darkened room with unnecessary electrical equipment turned off to avoid electromagnetic interference. Subjects were requested to lie relaxed with their eyes closed. Evoked Potentials (EPs) were recorded with open online filters and stored offline for analysis.

Prior to rectal evoked potential acquisition, median nerve somatosensory evoked potentials were recorded. Stimuli were delivered using two surface electrodes 2.5 cm apart, placed on the radial border of the volar aspect of the non-dominant forearm, 1 cm from the wrist crease. Stimuli were delivered at an intensity that evoked twitching of the thenar or flexor digitorum muscles (indicating electrical stimulation of the median nerve). Five hundred electrical stimuli were applied with square wave pulse of 0.2 ms duration at a frequency of 2 Hz.

Rectal evoked potentials were then recorded. Impedance between the electrodes was maintained below 3 k Ω . If impedance was >3 k Ω , or the subject did not report a perception of intra-rectal stimulation, a latex balloon mounted on a catheter was placed aside the electrode and inflated to 10 mls below sensation threshold to ensure good electrode apposition to the rectal wall. Recordings were obtained under the same conditions as somatosensory recordings.

As a large variation between sensory thresholds in patients and controls was expected, precluding the use of a standardised value, stimulus intensity was individualised and delivered at the subjects' pain threshold (Drewes *et al.*, 2004, Drewes *et al.*, 2006). This threshold was chosen in preference to maximal tolerable sensation (as used in some studies (Hobson *et al.*, 1998, Hobday *et al.*, 2002, Harris *et al.*, 2006)), as, given the patients' known hyposensitivity, it was predicted that maximal tolerable

sensation would not be reached in a proportion within the preset safety limit. Four sets of 50 electrical stimuli were applied with square wave pulse of 0.2 ms duration at a frequency of 0.2 Hz. Patients were asked to describe the location and sensation experienced during the stimulations.

14.2.2.1.1 Evoked potential pre-processing

All pre-processing was performed via neuroscan software (Neuroscan version 4.3.1; Neuroscan, El Paso, USA). For each of the four trials, data was band pass filtered between 0.5 – 200 Hz and epoched to 50 ms before, until 350 ms after the stimulus onset. Epochs were manually reviewed and those contaminated by eye movement were rejected. The remaining “clean” epochs were averaged. The best average trace of the four sets of stimuli was re-referenced to a linked ear reference for final analysis.

14.2.2.1.2 Evoked potential analysis

Analysis of EP latencies and amplitudes was performed from the central electrode (Cz). Peak amplitudes were consistently greatest at this electrode, in line with previously published literature (Hobday *et al.*, 2002). Peak latencies were determined as the time (ms) from stimulus to the mid-point of that peak. Peak amplitude was determined by peak-to-peak analysis.

14.2.2.2 Inverse modelling and topographical analysis

The EP analysis was guided by simultaneous topographic mapping based on spline interpolation (Michel *et al.*, 2004), which shows scalp distribution derived from all electrodes simultaneously. Topographical analysis was completed using the neuroscan software, and dipolar source modelling was performed using brain electrical source analysis (BESA) software (BESA Research 5.3, MEGIS Software GmbH, Gräfelfing, Germany). BESA uses evoked potential data to calculate potential voltage distributions over the scalp, and evaluates agreement between recorded and calculated field distributions in order to determine spatiotemporal activation of the brain in response to the stimuli. The percentage of data that cannot be explained by the model is expressed as residual variance (RV). A RV of less than 10% is considered to be a good fit (Maurits, 2011).

Grand mean data for each group was used for dipole source analysis. Current density analysis (LORETA algorithm) (Pascual-Marqui *et al.*, 2002) was employed to guide inverse modelling. LORETA is a current density method yielding blurred source images. The advantage of LORETA is that no *a priori* constraints regarding the number or location of sources are required. Its accuracy has been proven high (Pascual-Marqui *et al.*, 2002). Symmetric constraints were applied to the bilateral sources based on symmetry assumption between the two hemispheres. The latency interval from 40 ms pre-stimulus to 350 ms was used for analysis.

14.2.2.3 Statistical analysis

Descriptive statistics are reported as median (range), or mean (SD), where appropriate. Perceptual thresholds were analysed using Mann-Whitney U test. EP peak data were compared by analysis of variance (ANOVA). Contingency tables were analysed using Fishers exact test. A *P* value of <0.05 was considered statistically significant.

14.3 Results

All subjects underwent all tests without complication. However, four patients and two healthy volunteers were excluded from analysis, as a clear EP trace was unable to be recorded. The study cohort therefore comprised 11 healthy volunteers (9 female, median age 33, range 20 - 62) and 13 RH, (all female, median age 46, range 20 - 62). A tap water enema was administered to two patients. Five patients and one healthy volunteer required the placement of an intra-rectal balloon inflated to sub-sensory volume to optimise electrode-mucosa contact. All patients and volunteers had a normal neurological examination.

14.3.1 Clinical assessment

Symptom severity scores confirmed the presence of constipation in all patients with a median Cleveland constipation score of 14 (range 9 – 23). All healthy volunteers reported scores of less than 5 (Table 19, *P* <0.001), and denied any history of constipation.

14.3.2 Sensory assessment

14.3.2.1 Somatic

Sensory thresholds to peripheral electrical stimulation at the median nerve were similar between the two groups, as was the motor threshold (Table 19).

14.3.2.2 Rectal

All healthy volunteers had normal sensory thresholds to balloon distension. As expected, sensory thresholds were significantly higher in patients with RH (first constant sensation: $P = 0.016$; defaecatory desire volume: $P = <0.0001$; maximal tolerable volume: $P = <0.0002$) with all median values outside of departmental normal ranges (Table 19).

Sensory thresholds to rectal electrical stimulation were also significantly higher in the patient group (Table 19, first sensation: $P = 0.008$; pain threshold: $P = 0.007$; maximal tolerable sensation: $P = 0.05$). In four patients, pain threshold was not reached at the preset stimulation limit of 80 mA, and in three patients, maximum tolerable threshold was not reached. All healthy volunteers described pain threshold but two did not reach maximum tolerable sensation. Patients, in contrast to healthy volunteers, also described aberrant sensation, more commonly noting referred sensation to the legs / abdomen or obvious pelvic floor / anal sphincter contractions before pain threshold was reached ($n = 6$ vs. $n = 0$; $P = 0.01$).

TABLE 19 – COMPARISON OF CLINICAL AND SENSORY DATA BETWEEN PATIENTS WITH CONSTIPATION AND RECTAL HYPOSENSITIVITY (RH) AND HEALTHY VOLUNTEERS (HV) EXPRESSED AS MEDIAN RANGE

	HV (n=11)	RH (n=13)	P - value
Demographics			
Sex (female)	9	13	0.19
Age	33 (20-62)	46 (20-62)	0.24
Constipation symptom severity	HV	RH	P-value
Cleveland clinic constipation score	3 (0 - 5)	14 (9 - 23)	<0.0001
Sensation to balloon distension: mls			
First constant sensation	34 (12 - 85)	120 (30 - 230)	0.016
Defaecatory desire volume#	82 (57-146)	270 (210 - 360)	<0.0001
Maximum tolerated volume#	170 (99-290)	300 (255 - 360)	<0.0002
Sensation to rectal electrical stimulation: mA			
First sensation	9 (3 - 29)	26 (5 - 59)	0.008
Pain threshold	24 (10 - 55)	59 (23 - 80)*	0.007

	HV (n=11)	RH (n=13)	<i>P - value</i>
Maximum tolerated	44 (14 - 80)*	80 (32 - 80)*	0.05
Sensation to peripheral electrical stimulation: mAmp			
Perception threshold	2.3 (0.7-3)	2.3 (1.2-3.4)	0.283
Motor threshold	7.4 (4.2 – 9.6)	6.1 (4.3 – 11.5)	0.27

14.3.3 Somatosensory evoked potentials

(Table 20)

There were no differences between somatosensory EP morphology, latency (both groups had a first peak at 13.5 msec, $P = 0.5$), and amplitude (first peak 1.0 μV in patients, vs. 1.3 μV ; $P=0.1$)

TABLE 20 – COMPARISON OF SOMATOSENSORY EVOKED POTENTIAL LATENCIES AND AMPLITUDES BETWEEN HEALTHY INDIVIDUALS AND PATIENTS WITH CONSTIPATION AND RH

	HV	RH	
	Mean (SD)	Mean (SD)	<i>P-value</i>
Peak latency (ms)			
P14	13.5 ± 0.9	13.5 ± 0.7	0.5
N20	19.7 ± 1.3	19.2 ± 0.6	0.2
Peak amplitude (μV)			
P14	1.3 ± 1.3	1.0 ± 0.4	0.1
N20	1.8 ± 1.3	1.7 ± 0.6	1.0

14.3.4 Rectal evoked potential analysis

14.3.4.1 Morphology

In nine patients and nine healthy volunteers, the classical triphasic EP morphology (Hobday *et al.*, 2002, Harris *et al.*, 2006) was seen consisting of a P1 peak, followed by N1 and P2 peaks (see Figure 52). In four patients and two healthy volunteers, the P1 component was not identified.

14.3.4.2 Latency

The latency of N1 was significantly delayed in RH patients in comparison to healthy volunteers (142 ± 24 vs. 116 ± 15 ms; $P = 0.004$). The latencies of the P1 component were similar, but there was a tendency to a delay in the P2 component ($P = 0.07$) (Figure 52, Table 21). When patients who did not reach pain threshold ($n = 4$) were excluded from analysis, there remained a trend towards delayed N1 latency (132 ms vs. 116 ms, $P = 0.08$).

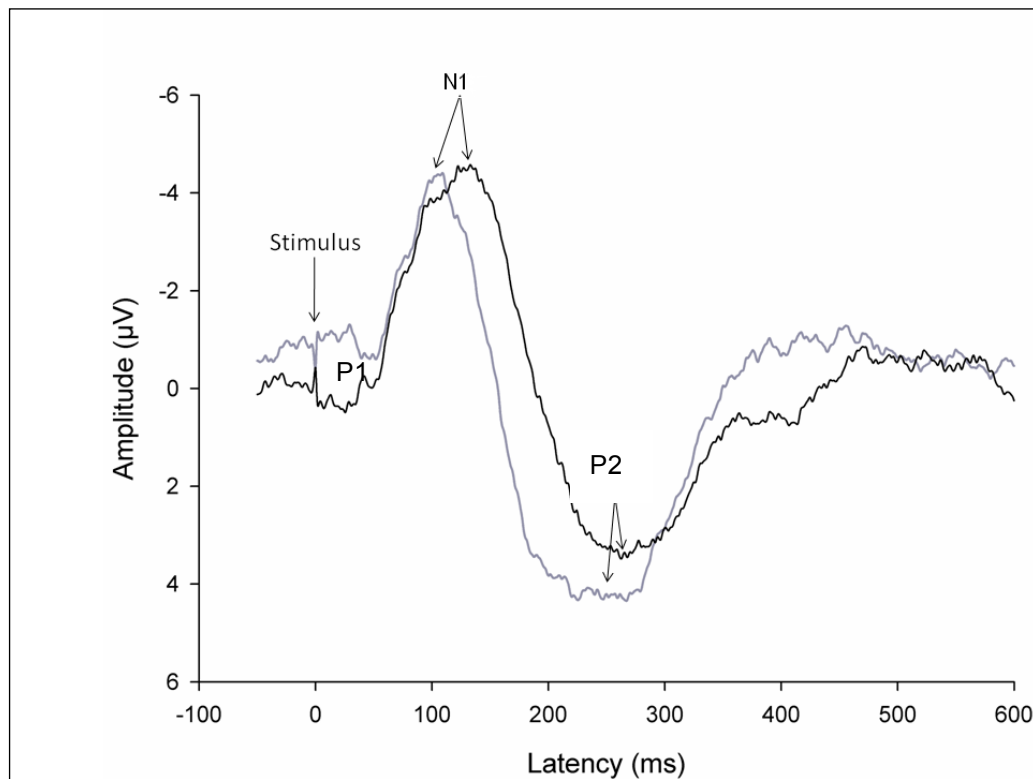


FIGURE 52 – EVOKED POTENTIAL TRACES TO RECTAL ELECTROSTIMULATION. GRAND MEAN TRACES FOR CONSTIPATED PATIENTS WITH RECTAL HYPOSENSITIVITY (BLACK LINE) AND HEALTHY VOLUNTEERS (GREY LINE) ARE SHOWN.

THE N1 COMPONENT WAS SIGNIFICANTLY PROLONGED WITHIN THE PATIENT GROUP ($P = 0.004$). THERE WAS A TENDENCY TO A DELAY IN P2 COMPONENT ($P = 0.07$).

14.3.4.3 Amplitude

Results are presented in Table 21. The P1 amplitude in patients tended to be of greater magnitude than that in controls ($3.3 \pm 2.7 \mu\text{V}$ vs. $1.2 \pm 0.8 \mu\text{V}$; $P = 0.05$). No other differences in peak-to-peak amplitudes were observed.

TABLE 21 – COMPARISON OF RECTAL EVOKED POTENTIAL LATENCY AND AMPLITUDE BETWEEN HEALTHY VOLUNTEERS AND PATIENTS WITH RH (*HV AND RH: N=9)

	HV Mean (\pm SD)	RH Mean (\pm SD)	<i>P-value</i>
Peak latency (ms)			
P1*	65 ± 13	78 ± 18	0.1
N1	116 ± 15	142 ± 24	0.004
P2	227 ± 31	250 ± 28	0.07
Peak amplitude (μV)			
Baseline – P1	1.2 ± 0.8	3.3 ± 2.7	0.05
P1 – N1	4.5 ± 3.0	4.9 ± 3.0	0.7
N1 – P2	12 ± 4.6	13.9 ± 9.4	0.6

14.3.4.4 Topographical analysis

The topographic pattern of activity was similar between and within groups ($P = 0.5$). The P1 component, when evident, was displayed bilaterally in the temporal areas, the N1 component was displayed in the temporal area and also centrally, and the later P2 component centrally (Figure 53A).

14.3.4.5 Dipole source modeling

In both patients and healthy volunteers, brain activity was localised bilaterally within the opercular regions (SII and insula) and the mid cingulate gyrus (Figure 53B). While there appeared to be no differences in cortical activation between groups, a delay in EP latency in patients was seen. Residual variance was 6.4% in the healthy volunteer model and 7.2% in the patient group.

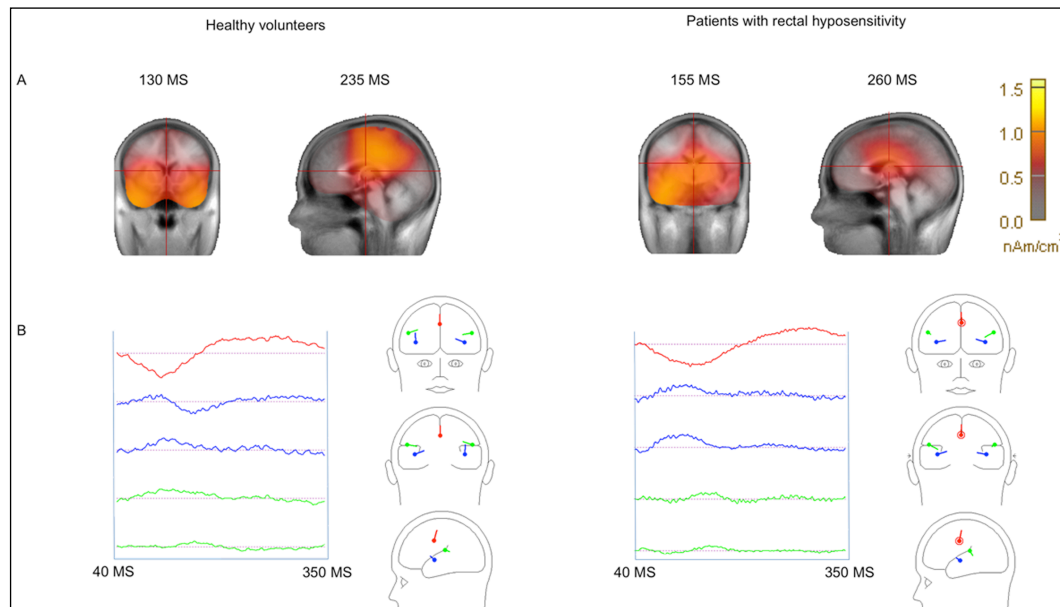


FIGURE 53 – SOURCE LOCALISATION RESULTS: A) TWO DISTINCT LORETA SOLUTIONS FOR THE EVOKED POTENTIAL AT TIME POINTS WHERE CURRENT DENSITY WAS THE HIGHEST. B) THE BESA MODEL BASED ON THE GRAND-MEAN.

THESE SOLUTIONS LIKELY REPRESENT UPPER SYLVIAN FISSURE (SII), LOWER SYLVIAN FISSURE (INSULA), AND ACTIVITY AROUND THE CENTRAL CINGULATE CORTEX. DIPOLAR SOURCES ARE SHOWN TO THE RIGHT AND THE WAVEFORMS TO THE LEFT SHOW THE SOURCE ACTIVITY OVER TIME. COLORS OF THE WAVEFORMS CORRESPOND TO COLOURS OF DIPOLAR SOURCES: RED – CINGULATE CORTEX; BLUE – INSULA; GREEN – SECONDARY SOMATOSENSORY CORTEX. THE BOX OVER THE WAVEFORMS IS THE TIME INTERVAL UNDER ANALYSIS.

14.4 Discussion

As shown previously in this thesis, rectal hyposensitivity is associated with hindgut dysfunction and symptom severity; however, the pathophysiology of impaired sensation remains unknown. One possible mechanism is that RH is secondary to afferent nerve dysfunction, with the site of this defect potentially occurring anywhere from the receptor level to the cerebral cortex. This study is the first to provide direct evidence of altered visceral nerve transmission in adult constipated patients, as evidenced by delayed EP latencies.

The current study is unique in helping to elucidate the localisation of the proposed afferent pathway defect. Electrical stimulation bypasses end-organ receptors and directly stimulates neuronal axons. Therefore any changes seen in evoked potential latencies are not an effect of aberrant receptor function alone (although a concurrent receptor defect cannot be excluded), but suggests abnormal peripheral or central nerve conduction. Subsequent modelling of cortical activity using inverse modelling of the EP data indicated there were no differences in areas of cortical activation, only a temporal delay. This has potential clinical implications as, unlike patients with irritable bowel syndrome, who have been shown to have altered cortical processing in inverse modelling and functional brain imaging studies (Mertz *et al.*, 2000, Drewes *et al.*, 2005, Elsenbruch *et al.*, 2010, Rapps *et al.*, 2008), these patients may be less likely to benefit from

psychoemotional therapeutic interventions designed to influence cortical function. Furthermore, the finding of similar peak latencies recorded from median nerve EPs suggests the neurological dysfunction is an isolated visceral phenomenon and not a generalised defect of sensory function.

Comparison with previous studies

Previously, EPs have been established in healthy control studies to be effective in measuring the integrity of the afferent nerve supply to the bowel, providing robust and temporally reproducible data (Hobday *et al.*, 2000, Hobday *et al.*, 2002, Harris *et al.*, 2006, Remes-Troche *et al.*, 2011). In the current study, traces were obtained with similar morphologies to those recorded in prior studies (Hobday *et al.*, 2000, Hobday *et al.*, 2002), with latencies at N1 and P2 within the ranges previously reported in healthy volunteers, though the amplitude of each peak was somewhat reduced. This may be a consequence of pain threshold, rather than maximal tolerated sensation being used to evoke the cortical potentials in this study. With regard to the patient group, only one prior study (published in abstract form only) has used a similar technique and reported cortical evoked potentials in patients with constipation allied to dyssynergic defaecation (Remes-Troche *et al.*, 2007). Similar results were found to those presented here, with increased sensory thresholds and prolonged EP latencies, providing further supportive evidence towards brain-gut axis dysfunction. Unfortunately, patients from Remes-Troche *et al.* were not stratified by sensory subtype. A similar study has also been carried out in

constipated children with encopresis (Loening-Baucke and Yamada, 1995). However, balloon, rather than electrical stimulation, was used to elicit EPs, and thus direct comparison of latencies was not possible. Nevertheless, that study did also show prolonged EP latencies in comparison to controls, suggesting afferent dysfunction. Rectal sensory status was, again, not reported, although it is recognised that up to two-thirds of chronically constipated children have RH (Meunier *et al.*, 1979).

In patients with the irritable bowel syndrome, which is commonly associated with rectal *hypersensitivity*, a *reduction* in EP latency has been reported (Chan *et al.*, 2001, Sinhamahapatra *et al.*, 2001). This has been hypothesised as due to: increased recruitment of mucosal receptors; earlier activation of afferent fibres; faster neuronal conduction; or altered cortical processing (Chan *et al.*, 2001). It is possible that the same mechanisms (albeit the inverse) explain the delay in latencies seen in the current study. In the *hyposensate* patient group, *increased* EP latencies may be a result of either reduced activation of afferent nerves or slowed peripheral neuronal conduction. Damage to the pelvic or spinal nerves as a result of childbirth (Snooks *et al.*, 1986), chronic straining at stool (Lubowski *et al.*, 1988), or surgery may perhaps be a contributing factor (Gladman *et al.*, 2003b, Scott and Lunniss, 2011). It is also possible that neuronal transmission may be influenced by alterations in cerebral outflow mediated via the extrinsic autonomic nerves (Emmanuel and Kamm, 2001). Notably, previous studies have suggested that patients with RH

have intact spinal reflexes (Remes-Troche *et al.*, 2010) as the recto-anal inhibitory reflex, recto-anal contractile response and sensorimotor response are preserved, though higher volumes of rectal distension are required to induce these responses. This suggests that any potential neuronal abnormality lies above the level of the reflex arc but below the cortex, as there was no difference in cortical processing on inverse modelling.

Methodological aspects

There are of course limitations to the techniques used within the study. Most obviously, electrical stimuli may not be considered physiological. The nerve supply to the rectum mostly consists of primary afferents comprising small myelinated A-delta fibres and non-myelinated C-fibres, both of which respond to rectal wall distension (Hobday *et al.*, 2000). Electrical stimulation results in non-specific activation of these fibres. The advantage of electric stimulation, however, is that it has a rapid on / off, thus producing better quality EPs than that of balloon distension. The stimulus is also better quantified than balloon distension, which is affected by rectal wall compliance. This is particularly important in patients with RH where altered rectal compliance commonly co-exists (Gladman *et al.*, 2005), or indeed may be causative. Finally, the morphology of EPs to electrical stimulation and distension of the rectum is similar, indicating activation of the same fibre population (Hobday *et al.*, 2000, Treede *et al.*, 2003).

The advantage of evaluating brain signals using evoked potentials is the excellent time resolution, being in the order of milliseconds, compared to other modalities such as functional Magnetic resonance imaging that has time resolutions in the order of seconds. The disadvantage of EPs, however, is their limited spatial resolution. Mathematical techniques attempt to overcome this, by estimating the brain sources generating the EPs, via inverse modelling. In this study, BESA was utilised. The model calculated by BESA is a hypothetical one and does not exclude other solutions, but nevertheless, it can be validated when applied to individual data and is consistent with anatomical and physiological knowledge of identified source areas (Valeriani *et al.*, 2001). Indeed, our inverse model fits with what has previously been found in the visceral evoked potential literature (Drewes *et al.*, 2004).

The accuracy of source localisation in this study is slightly compromised as individual head MRI data was not used, with analysis relied on a standard spherical head model. However, as patients with constipation are not considered a group at risk for structural cortical abnormalities the use of standard MRI data was not thought to significantly impact the results produced.

There is controversy as to the appropriate stimulation point within the rectum. In this study, to ensure the rectum (and not sigmoid colon) was being stimulated, the probe was placed at 10 cm from the anal verge. This

is consistent with a recent study, using electrodes attached to the rectal wall, which found the optimal stimulating distance to be between 8 – 16 cm (Garvin *et al.*, 2010) from the anal verge. Stimulation of the mid to upper rectum should preclude any involvement of the somatic nerves as Chan *et al* (Chan *et al.*, 2005b) showed that the pudendal nerve does not innervate the distal rectum until a level well below the site of stimulation. As with some (Frieling *et al.*, 1989, Olesen *et al.*, 2010) but not all (Loening-Baucke *et al.*, 1992) studies, triphasic or biphasic waveforms in both groups were recorded with onsets of 65 ± 13 ms for healthy controls and 78 ± 18 ms for the patients. This corresponds to previous findings (Hobday *et al.*, 2002, Olesen *et al.*, 2010, Harris *et al.*, 2006), and in contrast to Loening-Baucke *et al.*, (Loening-Baucke *et al.*, 1992) who reported an “early onset” multiphasic EP (20 – 30 ms: proposed to relate to the activation of somatosensory nerves), indicates that only visceral nerves were activated within the present study. Also consistent with other studies (Hobday *et al.*, 2000, Hobday *et al.*, 2002), P1 at the vertex was not observed in all subjects (absent in 31% of patients and 18% of healthy volunteers). Although this finding may be secondary to the analysis techniques utilised, as P1 is more easily seen in temporal electrodes.

Stimulation intensity also remains controversial. In this study, patients and volunteers were stimulated at pain threshold. This is a subjective measure, resulting in individualised stimulation intensities, and is consistent with all previous literature establishing visceral EPs in humans as an investigative

technique (Loening-Baucke *et al.*, 1992, Speakman *et al.*, 1993, Hobson *et al.*, 1998, Hobday *et al.*, 2000, Sinhamahapatra *et al.*, 2001, Hobday *et al.*, 2002, Drewes *et al.*, 2004, Drewes *et al.*, 2005, Drewes *et al.*, 2006). Nevertheless, it is appreciated that such an approach relies on the assumption that two individuals experience the same quality of sensation (although at different stimulation intensities), and it is known that visceral sensation is, of course, affected by mood, stress levels etc. (Sarkar *et al.*, 2000, Hobson *et al.*, 2006, Paine *et al.*, 2009, Coen *et al.*, 2011, Botha *et al.*, 2011). However a standardised stimulation intensity was not possible, as the mean pain threshold in patients was greater than the maximal tolerable sensation of healthy volunteers. Conversely, the intensity required to stimulate pain in healthy subjects would have been sub-sensory in almost 50% of the patients with RH. This was expected as by definition patients with RH have elevated sensory thresholds to rectal stimulation, which in the majority involve all modalities (Gladman *et al.*, 2009). For example, patients with RH have a mean DDV that is greater than the mean MTV of healthy volunteers and patients with normal sensation. Use of individualised stimulation intensity was thus considered valid (though is accepted as an unavoidable limitation of the investigative technique).

Subjects

As expected, heterogeneity existed within the patient group in this study. Consistent with earlier work (Gladman *et al.*, 2009), it was found that a

small number of patients ($n = 4$) did not have elevated electrical thresholds despite elevated balloon distension volumes. In these patients, altered biomechanics of the rectal wall would likely account for the finding of hyposensitivity to simple balloon distension. It would be expected therefore that recorded EP latencies in these subjects would be similar to healthy controls and indeed there was a trend towards this. However, the sample size was too small for it to be substantiated.

Also, despite attempts to avoid variation in stimulation intensity by using the individualised pain threshold, four patients did not reach this level by the previously set safety cut off, and thus EPs were recorded at lower subjective intensity than in healthy individuals. This may provide an alternative explanation for the finding of delayed EP latencies in the RH group. Prior studies show, as subjective appreciation of the intensity of stimulation increases, EP latency decreases (Hobson *et al.*, 1998). Nevertheless, when patients not stimulated at pain threshold were excluded from analysis, there still remained a clear trend towards a delay in EP latency.

Patients were also more likely to report aberrant sensations (i.e. referred sensation or anal motor contraction) in response to rectal stimulation. This may be due to the higher stimulus intensity required in patients than volunteers, which would increase the field of stimulation, perhaps recruiting nerves lying outside the rectum before rectal thresholds were

reached. While this raises the possibility that somatic nerves were also stimulated in these individuals, this should not influence the outcome of the study. Somatosensory evoked potentials from the lower limb or pelvis are usually detected within a time frame of 60 ms (Loening-Baucke *et al.*, 1991, Loening-Baucke *et al.*, 1992, Leeman, 2007) whereas onset of visceral evoked potentials, as seen in this study, tends to be found beyond this point (Hobday *et al.*, 2002, Harris *et al.*, 2006).

14.5 Conclusions

This exploratory mechanistic study is the first to provide evidence of impairment of visceral nerve function in patients with constipation and RH. Prolonged peak latencies in such patients suggest defective neuronal conduction, while cerebral cortical processing of visceral sensory information seems normal. This adds further weight to the hypothesis that afferent nerve dysfunction is important in the development of functional hindgut disorders.

15 ASSESSMENT OF THE NEURONAL PATHWAYS TO THE ANORECTUM IN HEALTH AND IN PATIENTS WITH CONSTIPATION STRATIFIED BY RECTAL SENSORY STATUS

15.1 Introduction

Constipation is a heterogeneous disorder with varying causes and (probable overlapping) pathophysiologies. However, in a proportion of patients, primary neuronal dysfunction appears likely. It is feasible that altered (blunted) rectal sensation may provide a physiological marker for such a process. Direct assessment of afferent pathways from the rectum (Chapter 14) suggests that patients with constipation and Rectal hyposensitivity (RH) may have abnormal transmission of sensory information, with slowing of evoked potential latencies in comparison to healthy controls; however whether this is a localised process or part of a systemic pathology is unknown.

Although rectal hyposensitivity (RH) has been shown to be clinically important (Chapters 11, 12 and 13), the mechanisms underscoring blunted rectal sensation remain undefined. RH was first described following parasympathetic block prior to surgery (Goligher and Hughes, 1951) and was subsequently reported in patients with anorectal dysfunction secondary to supraconal spinal cord injuries (Sun *et al.*, 1990a, MacDonagh *et al.*, 1992, Greving *et al.*, 1998) and generalised

neuropathic disorders (Caruana *et al.*, 1991, Nordenbo *et al.*, 1996) suggesting a potential mechanistic association.

However, in other patients with hindgut dysfunction, notably chronic constipation (Shouler and Keighley, 1986, Varma and Smith, 1988) and faecal incontinence (Hancke and Schurholz, 1987, Speakman and Kamm, 1993, Gladman *et al.*, 2003a), the majority of patients with RH do not have overt neurological disease, suggesting other more complex pathoaetiologies, or alternatively, lack of adequate diagnostic techniques.

Acquired pelvic nerve damage has been proposed as a cause of constipation and indeed, many patients describe pelvic surgery or childbirth as a precipitant for their symptoms (Snooks *et al.*, 1986, Snooks *et al.*, 1990). The potential mechanistic association between pelvic nerve damage and RH is supported by the preliminary work that demonstrated that patients with constipation and rectal hyposensitivity also have bladder sensory dysfunction, suggesting a pan-pelvic enteric neuropathy (Gladman *et al.*, 2004). If pelvic nerve damage does underlie symptoms of constipation, it is reasonable to expect that the pathology may affect both motor and sensory domains, given the common motor and sensory innervation (Berthoud *et al.*, 2004) although this has never been objectively tested.

Nevertheless, other emerging evidence indicates that, at least in a proportion of sufferers, a primary (as yet undefined) neuropathic disorder (Bassotti and Villanacci, 2006) may underlie the symptoms of constipation. While the focus of research has been directed to abnormalities of enteric motor function, with such patients being found to have alterations in the number of enteric neurons and supporting cells in the colon on immunohistological techniques (Schouten *et al.*, 1993, Bassotti *et al.*, 2006, Knowles *et al.*, 2013), smaller studies have also shown that constipation may be associated with a systemic sensory neuropathy, with autonomic and small fibre sensory dysfunction demonstrated (Raethjen *et al.*, 1997, Knowles *et al.*, 1999). It is thus possible that, rather than a marker of acquired pelvic nerve damage, blunted rectal sensation may instead represent a more generalised neuropathic disorder. To date however, a thorough assessment of both somatic and visceral afferent and efferent function, using contemporary methodologies has not been performed in patients with chronic constipation.

Determining whether the physiological finding of RH is the hallmark of an occult neuropathic process, either systemic or localised, will provide valuable information for developing future therapies. Determining the mechanisms by which visceral afferent function becomes disturbed is also likely to be critical to prognosis and management of patients.

Evoked potential recordings have emerged as a useful technique to assess the transmission of afferent information from the viscera and have been used in a number of studies to formally interrogate afferent pathways in patients with hindgut dysfunction (Hobday *et al.*, 2000, Rossel *et al.*, 2001, Hobday *et al.*, 2002, Drewes *et al.*, 2004, Arebi *et al.*, 2011, Remes-Troche *et al.*, 2011). Until recently, however, there has been limited information available as to the descending control of the anorectum. Motor evoked potentials following magnetic stimulation of the cortex and lumbosacral nerve roots is a non-invasive and essentially painless technique that has been developed to assess these pathways (Hamdy *et al.*, 1998, Welter *et al.*, 2000, Harris *et al.*, 2008, Remes-Troche *et al.*, 2011, Tantiphlachiva *et al.*, 2011, Coss-Adame *et al.*, 2012). Magnetic stimulation, via electromagnetic induction, results in the activation of cortical or lumbosacral neurones leading to contraction of the dependent muscle group. It has been shown to be reproducible (Remes-Troche *et al.*, 2011) and has been used successfully to detect efferent pathway abnormalities in patients with hindgut disorders (Tantiphlachiva *et al.*, 2011, Coss-Adame *et al.*, 2012). Analysis of latencies (time between stimulus and response) for both rectal evoked potentials and motor evoked potentials following magnetic stimulation provides assessment of the integrity of sensory (Hobday *et al.*, 2000) and motor pathways (Chen *et al.*, 2008), respectively.

The aim of this exploratory pilot study is to examine whether in patients with constipation, RH is associated with concurrent efferent or somatic neuronal dysfunction. To achieve this, patients with RH were compared to subjects with constipation and normal rectal sensation, and also healthy volunteers, all of whom underwent comprehensive testing of visceral and peripheral sensory function in both sacral and cervical dermatomes, and assessment of efferent and afferent neuronal transmission using magnetic stimulation and rectal evoked potentials.

15.2 Methods

15.2.1 Clinical assessment

Patients with constipation were recruited from those undergoing anorectal physiological investigations within the GI Physiology Unit at the Royal London Hospital. The study protocol was approved by the City and East London Alpha Ethics Committee (ref no. 10/H0704/11). All subjects provided signed informed consent prior to entering into the study.

Patients were eligible for inclusion if they described a history of constipation defined as “unsatisfactory defaecation characterized by infrequent stools, difficult stool passage or both, at least for the previous 3 months and where appropriate investigations have occurred and a secondary cause excluded” (American College of Gastroenterology Chronic Constipation Task Force, 2005b). Exclusion criteria included:

neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease, previous spinal surgery, spinal injuries including spinal cord transection, congenital anorectal anomalies or absence of native rectum due to surgery, external full-thickness rectal prolapse, previous rectal surgery, stoma *in situ*, chronic bowel diseases such as inflammatory bowel disease, epilepsy, or contraindication to magnetic stimulation (i.e. metallic implant, hearing impairment), pregnancy or intention to become pregnant.

All subjects underwent standard anorectal physiological investigations, including rectal sensory testing using latex balloon distension, anorectal manometry, and endo-anal ultrasound as described in detail in Chapter 10. All patients also underwent proctographic examination, and assessment of colonic transit using radio-opaque markers (in the majority), as part of their clinical workup. Patients were excluded if they were found to have increased rectal dimensions on proctography (i.e. a megarectum). All subjects then underwent barostat examination and mucosal electrical sensory testing to carefully stratify patients on the basis of rectal sensation (Kamm and Lennard-Jones, 1990, Gladman *et al.*, 2005, Scott and Gladman, 2008) into those with normal sensation (NS) or those with rectal hyposensitivity (RH). The latter was defined by the presence of two or more elevated sensory thresholds within either of these sensory modalities (barostat = first constant sensation pressure [FCSp], defaecatory desire pressure [DDP] or maximal tolerable pressure [MTP]; electrical sensory

thresholds = first sensation [FS], pain detection threshold [PDT] or maximal tolerable sensation [MTS]; normal values obtained from healthy volunteers). Patients found to have hypercompliance or increased rectal dimensions (megarectum) on rectal barostat testing during the study were also excluded from final analysis to minimise the confounding effects of rectal wall biomechanical changes on sensory function (Gladman *et al.*, 2009).

All subjects completed validated questionnaires (Chapter 10) to assess severity of constipation (Cleveland Clinic constipation score: [CCCS], 0 - 30) and incontinence symptoms (St Mark's incontinence score: [SMIS], 0 - 24), as well as clinician-directed history targeted at symptoms of evacuatory dysfunction and constipation. Past medical history, family history, medication history and obstetric history were also recorded.

Subjects presented for examination after an overnight fast. They were instructed to withhold all bowel medications for at least 24 hours. The examination was conducted in a quiet private room by the study investigator with a chaperone present. All subjects underwent a detailed full upper limb, lower limb and cranial nerve neurological examination. No bowel preparation was routinely utilised; however, prior to commencing the study, a digital rectal examination was performed and if residual faeces were noted, a warm tap water enema was performed until the effluent was clear.

15.2.2 Visceral sensory testing

15.2.2.1 Barostat

Visceral afferent function and rectal biomechanics were assessed using a computer-controlled barostat (Distender II; G&J Electronic inc. Toronto Canada) connected to an infinitely compliant pillow-shaped bag 10 cm in length (Mui Scientific. Toronto. Canada), with a maximal volume of 600 ml, connected to the distal end of a dual-lumen PVC catheter. The catheter was connected to the barostat assembly via an inflation channel and pressure transducer.

Examination was carried out in the left lateral position. The barostat bag was inserted into the rectum so that the centre of the bag was placed 10 cm from the anal verge. The barostat bag was then manually inflated to 120 ml to ensure adequate unfolding, before the system was opened to atmosphere prior to connection to the barostat system.

15.2.2.1.1 *Conditioning distension*

To familiarize the subject with the procedure and to enhance reproducibility, a conditioning distension was performed by inflating the barostat bag from 0 – 20 mmHg (or until maximal tolerable sensation was reached) in 4 mmHg increments over 30 seconds intervals (Figure 54).

15.2.2.1.2 Minimal distending pressure

Minimal distending pressure was performed by inflating the barostat bag in 1 mmHg increments over 60 second intervals until the point at which clear respiratory variations were seen on the volume trace (Figure 54).

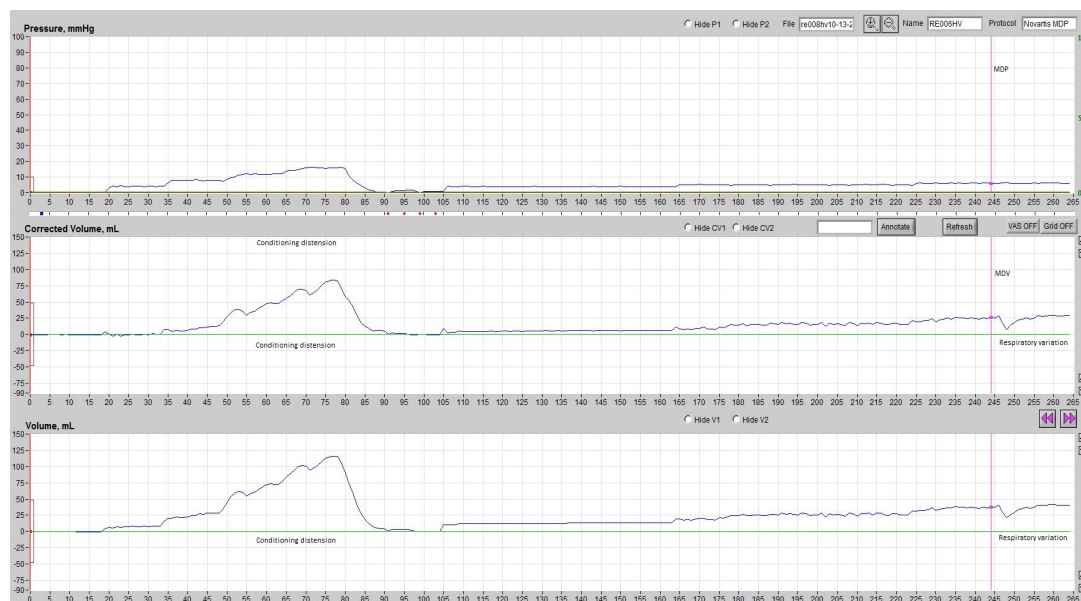


FIGURE 54 – BAROSTAT TRACE RECORDED DURING CONDITIONING DISTENSION AND DETERMINATION OF MINIMAL DISTENDING VOLUME (MDV) AND PRESSURE (MDP) IN A HEALTHY VOLUNTEER.

MDP AND MDV ARE THE PRESSURE AND VOLUME, RESPECTIVELY, AT WHICH RESPIRATORY EXCURSIONS CAN BE SEEN ON THE VOLUME TRACE (HIGHLIGHTED ABOVE - PINK LINE). THIS REPRESENTS THE POINT AT WHICH THE BAG HAS INFLATED TO FILL, BUT NOT DISTEND, THE RECTAL LUMEN. X-AXIS = TIME (SECONDS).

15.2.2.1.3 Sensory threshold testing

Sensory threshold testing was performed using a cumulative stepwise ascending methods of limits protocol with 4 mmHg pressure increments (Figure 55). The barostat bag was inflated for 60 seconds intervals at each pressure level. Subjects were instructed to inform the investigator when first sensation was experienced, the point at which defaecatory urge was induced, and at maximal tolerable sensation.

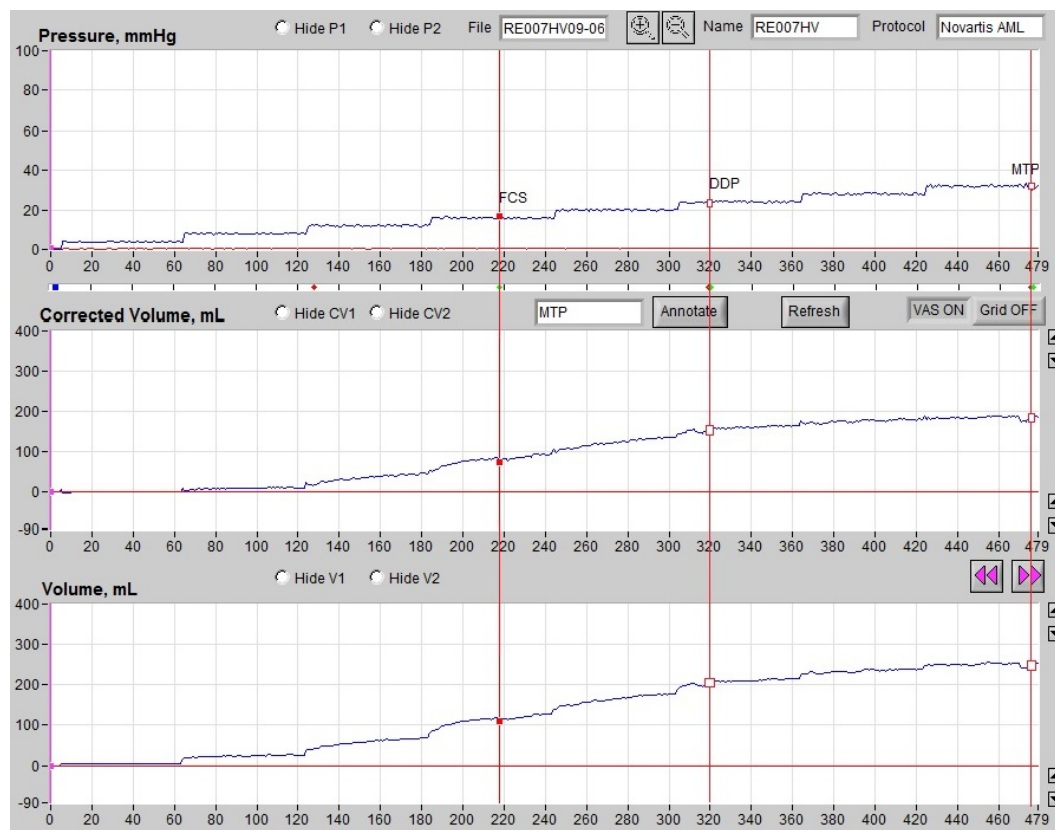


FIGURE 55 – REPRESENTATIVE EXAMPLE OF A BAROSTAT TRACE PERFORMED IN A HEALTHY VOLUNTEER.

PRESSURE AND VOLUME RECORDINGS WERE OBTAINED FOR FIRST CONSTANT SENSATION (FCS), DEFAECATORY DESIRE PRESSURE (DDP) AND MAXIMAL TOLERABLE PRESSURE (MTP). X-AXIS = TIME (SECONDS)

15.2.2.1.4 Rectal wall compliance

Pressure–volume curves were constructed from data collected during the ascending methods of limits protocol. Compliance was calculated as $\Delta V / \Delta P$ ml /mmHg⁻¹ (Gladman *et al.*, 2009).

15.2.2.2 Rectal mucosal electrosensitivity

A custom built catheter (Gaeltec Ltd, Isle of Skye. Scotland), with bipolar electrodes spaced 1 cm apart mounted on its tip, was inserted into the rectum so that the stimulating electrode was located 10 cm from the anal verge. Impedance between the electrodes was recorded, and the catheter was repositioned if the impedance was $>3\Omega$. If adequate impedance was not obtained, a rectal examination was performed to ensure the catheter was not coiled in the rectum. A balloon catheter was then placed alongside the stimulating electrode and inflated to 10 ml below FCS to ensure apposition. Stimulation was then performed via the Neuropack system (Nihon Kohden, United Kingdom; Surrey, UK) with a 0.2 ms square wave pulse at 1 Hz in 2 mA increments. Subjects were instructed to report first sensation, pain threshold and maximal tolerable sensation.

15.2.3 Assessment of somatic sensory function

15.2.3.1 Assessment of light touch

Light touch (Mechanical detection threshold) assessment was performed against the dorsum of hand (C6/C7 dermatome) and over the sacrum

superior to the natal cleft (S1/S2 dermatome) using standardised Von Frey Hairs (Somedic; Horby, Sweden), consisting of microfilaments of increasing diameter, where the force required to buckle the monofilament increases from 0.026 g to 110 g across the range within a set (corresponding to a pressure range of 5 g/mm² to 178 g/mm²). Patients were asked to report when they were aware of sensation in the area being tested. The filaments, using a method of levels technique, were incrementally applied to the testing area until sensation was detected (Rolke *et al.*, 2006). At that point, filaments with ascending and descending stimulus intensities were applied. Sensory threshold to light touch was determined by the lowest ranked filament at which sensation was consistently experienced. Light touch testing provides a robust measure of A β – sensory fibre function.

15.2.3.2 Assessment of pressure pain threshold

Pressure pain threshold was measured using a pressure algometer (Somedic, Horby, Sweden) that accurately quantifies pressure (kPa) required to induce a painful sensation. Testing was performed over the dorsum of hand (C6/C7 dermatome) and over the sacrum superior to the natal cleft (S1/S2 dermatome) using a 1 cm plate. Three trials were performed and the average taken as the result (Rolke *et al.*, 2006). Pressure pain threshold is the only modality known to measure deep somatic tissue pain response (Mainka *et al.*, 2014). It is mediated by a combination of C – fibres and A δ – fibres (Rolke *et al.*, 2006).

15.2.3.3 Assessment of electrical stimulation threshold

Electrical threshold testing also was also performed over the median nerve and in the S1/S2 dermatomes above the natal cleft. Stimulation was delivered using a 0.2 msec square wave pulse at a frequency of 2 Hz. On each examination, patients were asked to report at which point awareness of sensation occurred.

15.2.4 Assessment of afferent neuronal function

15.2.4.1 Evoked potentials

Electroencephalograph (EEG) signals were recorded from five silver chloride electrodes (Nihon Kohden) (Fz, Cz, Pz, CP3 and CP4) using the 10-20 system montage referenced to the right ear electrode, grounded to the alternate ear. Electro-conductive gel (Ten20 Conductive Neurodiagnostic Paste, Compumedics, Charlotte, USA) was applied to each electrode ensuring good contact between them and the scalp. Inter-electrode impedances were monitored and kept below 10 k Ω at all sites. Recordings were obtained in a darkened room with unnecessary electrical equipment turned off to avoid electromagnetic interference. Subjects were requested to lie relaxed with their eyes open. EPs were recorded with a bandpass filter of 0.1 – 100 Hz, with a 50 Hz notch filter, to minimize interference from mains electrical supply. The recording epoch was 1 second in duration of which 100 msec was pre-stimulus.

Prior to rectal evoked potential acquisition, median nerve somatosensory evoked potentials were recorded. Stimuli were delivered using two surface electrodes 2.5 cm apart, placed on the radial border of the volar aspect of the non-dominant forearm, 1 cm from the wrist crease. Stimuli were delivered at an intensity that evoked twitching of the thenar or flexor digitorum muscles (indicating electrical stimulation of the median nerve). Five hundred electrical stimuli were applied with square wave pulse of 0.2 ms duration at a frequency of 2 Hz.

Rectal evoked potentials were then recorded. Recordings were obtained under the same conditions as somatosensory recordings. As noted previously (Chapter 14), stimulus intensity was individualised and delivered at pain threshold (Drewes *et al.*, 2004, Drewes *et al.*, 2006) in an attempt to maximise the likelihood of a successful EP recording (given RH patients' known hyposensitivity, it was predicted that MTS would not be reached in a proportion given the preset safety limit (100mA)). Two sets of 50 electrical stimuli were applied with a square wave pulse of 0.2 ms duration and a frequency of 0.2 Hz, administered via a constant-current, high-voltage stimulator.

Patients were asked to describe the location and sensation experienced during the stimulations. EP latencies and amplitudes were determined by agreement of two independent assessors.

15.2.5 Assessment of hindgut motor function

15.2.5.1 Manometry

Station pull-through anorectal manometry was performed using a water perfused single-channel probe as described previously (Chapter 10).

15.2.5.2 Proctographic assessment

All patients (RH and NS) underwent proctographic assessment as part of their clinical investigation. The results of completeness of evacuation (%), duration of evacuation (seconds) and presence of any significant anatomical obstructive feature (e.g. intussusceptae or rectocoele) were compared between sensory groups.

15.2.5.3 Colonic transit study

All but four patients underwent colonic transit assessment using radio opaque-markers (as described in Chapter 10) as part of their clinical workup. The incidence of slow colonic transit was compared between groups as a surrogate marker for the presence of colonic motor dysfunction.

15.2.6 Assessment of efferent neuronal function

15.2.6.1 Anal EMG

Electromyogram response was recorded from the anal canal using an anal sponge electrode (Synectics Medical Limited. Enfield UK) (Sorensen *et al.*,

1991) inserted into the anal canal with a ground electrode on the right thigh. The electrode was inserted into the anal canal with a small amount of lubricant so that the electrodes were positioned at 3 and 9 o'clock. Subjects were left to rest until the EMG had stabilized. The EMG produced was amplified and recorded using the Neuropack system described above.

15.2.6.2 Lumbosacral magnetic stimulation

Single pulse lumbosacral magnetic stimulation (LSMS) was performed over the sacral nerve roots using a 70 mm outer diameter figure 8 coil powered by a magnetic stimulating device (Magstim 200; Magstim Co. Ltd, Carmarthenshire, UK). With the patient lying in the left lateral position, the stimulator was placed 9 cm above the coccyx in line with the natal cleft approximating to the S2 nerve root. Starting at 30% of the output of the stimulator, the stimulating coil was gradually repositioned with increasing stimulation intensities until an EMG of at least 10uV in 50% of stimulations was recorded. This defined the resting motor threshold (RMT). Ten stimulations were then performed at 10% above the RMT with each individual EMG response recorded for analysis.

15.2.6.3 Cortical magnetic stimulation

Cortical magnetic stimulation (CMS) was performed using a double cone coil placed over the vertex of the head (equivalent to Cz) with the patient seated. The scalp was stimulated at multiple points on and around the

vertex in approximately 1 cm increments, while gradually increasing the stimulator intensity as described for the lumbosacral stimulations (starting from a baseline of 30%) until a site was located in which a consistent discernible motor evoked potential was recorded (Remes-Troche *et al.*, 2011). Motor threshold was the stimulation intensity at which 50% of stimulations resulted in an EMG of greater than 10 μ V. Ten stimulations were then performed at 10% above the RMT with each individual EMG response recorded for analysis

15.3 Results

Fifteen healthy volunteers (all female, median age 42, range 29 – 59) and 21 patients with constipation (all female, median age 46, range 21 – 68) were recruited.

Following barostat and mucosal electrical sensitivity testing, patients were stratified into those with normal sensation (NS, $n = 8$) or rectal hyposensitivity (RH, $n = 12$) (Figure 56, Figure 57). One patient had abnormal rectal biomechanics (minimal distending volume of 81 ml [upper limit of normal 72 mls] indicating probable megarectum (Gladman *et al.*, 2007) and was excluded from further analysis, leaving 20 patients for analysis.

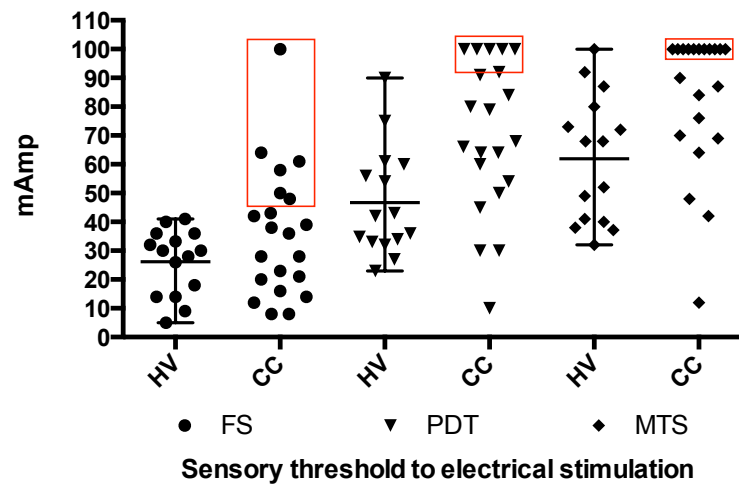


FIGURE 56 – SENSORY THRESHOLDS IN HEALTHY VOLUNTEERS AND PATIENTS TO ELECTRICAL STIMULATION

ERROR BARS FOR HEALTHY CONTROLS REPRESENTS MEAN +/- RANGE. ABNORMAL (HYPOSENSITIVE) THRESHOLDS ARE ENCLOSED WITHIN RED RECTANGLES. FS = FIRST SENSATION, PDT = PAIN DETECTION THRESHOLD, MTS = MAXIMAL TOLERABLE SENSATION

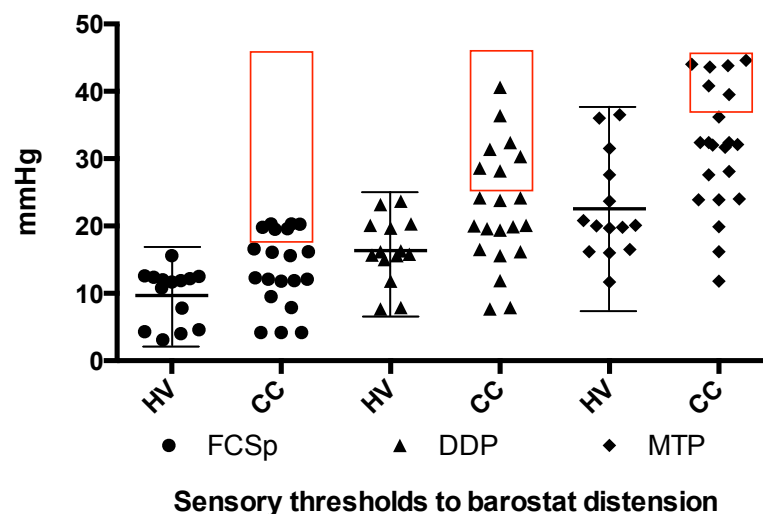


FIGURE 57 – SENSORY THRESHOLDS IN HEALTHY VOLUNTEERS AND PATIENTS TO BAROSTAT DISTENSION.

ERROR BARS FOR HEALTHY CONTROLS REPRESENTS MEAN +/- RANGE. ABNORMAL (HYPOSENSITIVE) THRESHOLDS ARE ENCLOSED WITHIN RED RECTANGLES., FCSp = FIRST CONSTANT SENSATION PRESSURE, DDP = DEFAECATORY DESIRE PRESSURE, MTP = MAXIMAL TOLERABLE PRESSURE.

Patients had significantly greater Cleveland Clinic constipation scores than healthy controls (mean CCCS, HV = 2 vs. patients = 16; $P < 0.0001$) but there was no difference in severity of symptoms between those with NS and RH (both reported mean CCCS of 16; $P = 0.9$). Patients also reported a higher St Mark's incontinence score (mean SMIS, HV = 2 vs. patients = 7; $P < 0.0001$) but there was no difference in symptom severity between sensory subtypes (mean SMIS, NS = 8 vs. RH = 6; $P = 0.23$)

Three patients with RH were nulliparous, as were two patients with NS and 7 healthy controls. Healthy volunteers had a median (range) height of 163 cm (152 – 174 cm), NS = 159 cm (154 – 170 cm) and RH = 160 cm (151 – 169 cm) ($P = 0.3$). Median (range) BMI was HV = 25.6 (21.2 – 36.8), NS = 25.6 (22.1 – 30.1) and RH = 25.7 (16.1 – 37.8) ($P = 0.9$). All subjects had a normal general neurological examination. Sixty-three percent of patients with normal rectal sensation described a precipitant for their symptoms, whereas only 40% of patients with RH could similarly do so (Table 22) ($P = 0.65$).

TABLE 22 – VOLUNTEERED PRECIPITANTS FOR SYMPTOMS AS DESCRIBED BY SUBJECTS (NUMBER) WITH CONSTIPATION AND NORMAL SENSATION (NS) AND CONSTIPATION AND RECTAL HYPOSENSITIVITY (RH)

Potential precipitant	NS (N = 8)	RH (N = 12)
Childbirth	2	1
History of psychological, physical or sexual abuse	1	1
Pelvic surgery	1	0
Post GI infection	0	2
Other (menopause, failure to pass meconium, lifestyle change)	1	1

Rectal wall biomechanical function was similar between all groups (mean compliance 12 mls/mmHg vs. 10 mls/mmHg vs. 10 mls/mmHg, HV, NS and RH respectively; $P = 0.5$), with no difference in minimal distending volume. However, patients with RH did have significantly higher pressure and volume sensory thresholds to barostat examination (all $P < 0.05$)

(Figure 58, Figure 59, Table 23)

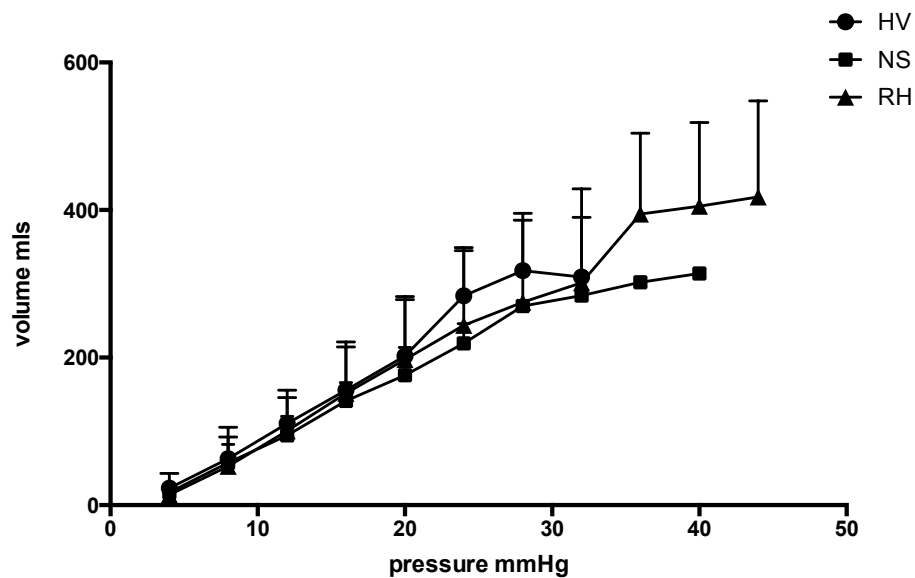


FIGURE 58 – PRESSURE VOLUME (MEAN SD) RELATIONSHIP IN HEALTHY VOLUNTEERS AND PATIENTS STRATIFIED BY RECTAL SENSORY STATUS

($P=0.48$).

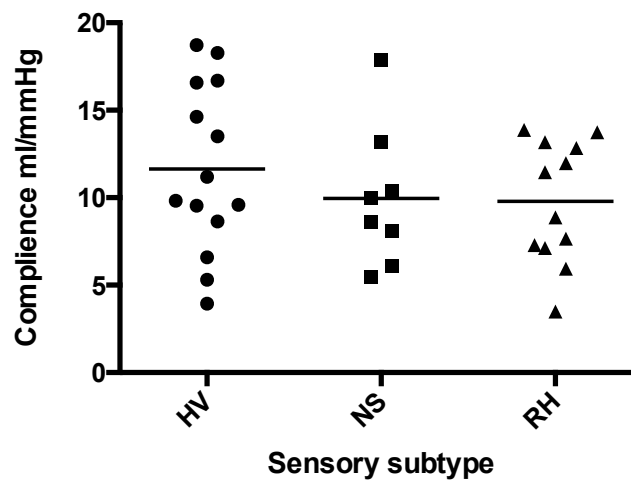


FIGURE 59 – RECTAL COMPLIANCE (MEAN) IN HEALTHY VOLUNTEERS AND PATIENTS STRATIFIED BY RECTAL SENSORY STATUS.

THERE WAS NO DIFFERENCE ACROSS ALL THREE GROUPS ($P = 0.48$)

TABLE 23 – COMPARISON OF BAROSTAT DATA (MEAN +/- SD) BETWEEN HEALTHY CONTROLS AND CONSTIPATED PATIENTS STRATIFIED BY RECTAL SENSORY STATUS.

	HV	NS	RH	P- value
Compliance	12 +/- 5	10 +/- 4	10 +/- 3	0.48
First sensation pressure (mmHg)	10 +/- 4	9 +/- 5	17 +/- 4	0.0001
Defaecatory desire pressure (mmHg)	16 +/- 5	15 +/- 5	28 +/- 7	<0.0001
Maximal tolerable pressure (mmHg)	23 +/- 8	24 +/- 9	37 +/- 6	0.0002
Minimal distending volume (mls)	36 +/- 20	31 +/- 14	27 +/- 21	0.45
First sensation volume (mls)	65 +/- 27	62 +/- 44	146 +/- 68	0.0003
Defaecatory desire volume (mls)	140 +/- 59	137 +/- 59	262 +/- 130	0.003
Maximal tolerable volume (mls)	232 +/- 94	214 +/- 88	336 +/- 128	0.02

RED LINE = UPPER LIMIT OF NORMAL DETERMINED FROM HV DATA. INDIVIDUAL PATIENT IDENTIFICATION CODES RECORDED FOR THOSE WITH ABNORMAL SENSORY THRESHOLDS TO ALLOW COMPARISON ACROSS MODALITIES

Patients with RH had also significantly higher pressure pain thresholds than HV ($P=0.02$), but not NS ($P=0.17$). There was no difference between patients with NS and healthy volunteers ($P=0.83$). One patient with normal rectal sensation and one patient with RH had thresholds at the upper limit of normal.

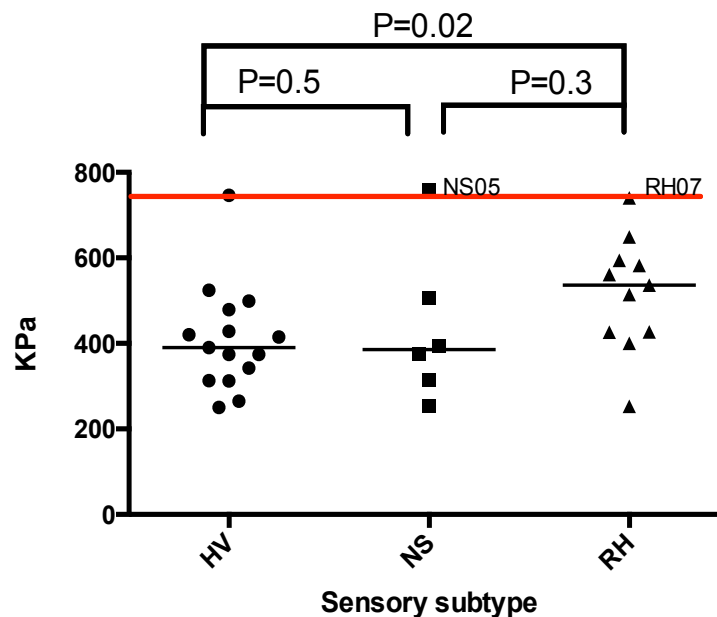


FIGURE 61 – PRESSURE PAIN THRESHOLD IN THE S1/S2 DERMATOME TO PRESSURE MEASURED IN KPA IN HEALTHY VOLUNTEERS (MEDIAN SHOWN) AND CONSTIPATED PATIENTS STRATIFIED BY RECTAL SENSORY STATUS.

RED LINE = UPPER LIMIT OF NORMAL DETERMINED FROM HV DATA. INDIVIDUAL PATIENT IDENTIFICATION CODES RECORDED FOR THOSE WITH ABNORMAL SENSORY THRESHOLDS TO ALLOW COMPARISON ACROSS MODALITIES

15.3.1.1.2 Electrical stimulation

Patients with RH had significantly higher sacral dermatome electrical stimulation thresholds than those with NS ($P=0.01$) but not HV ($P=0.1$) (Figure 62). One patient with RH had a markedly elevated sensory threshold; this same patient (RH06) also reported elevated thresholds to light touch and borderline levels to painful pressure.

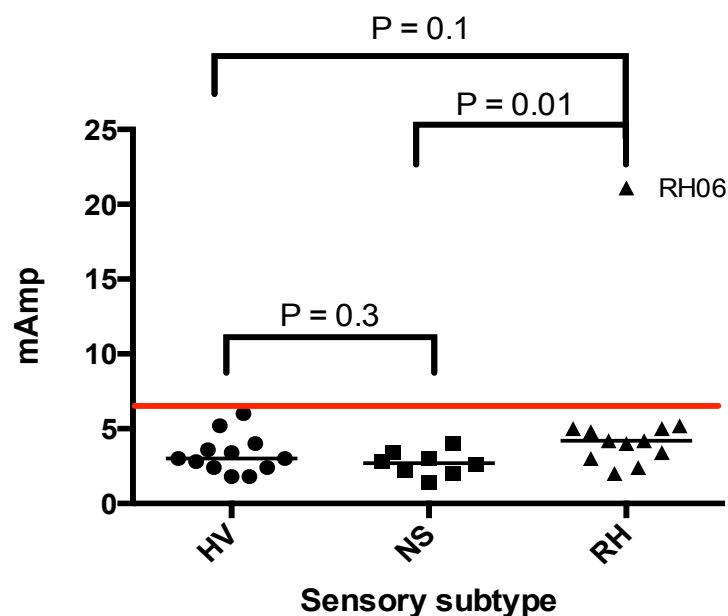


FIGURE 62 – SENSATION THRESHOLD (MEDIAN SHOWN) AT THE S1/S2 DERMATOME TO ELECTRICAL STIMULATION IN HEALTHY VOLUNTEERS AND PATIENTS STRATIFIED BY SENSORY STATUS

RED LINE = UPPER LIMIT OF NORMAL DETERMINED FROM HV DATA. INDIVIDUAL PATIENT IDENTIFICATION CODES RECORDED FOR THOSE WITH ABNORMAL SENSORY THRESHOLDS TO ALLOW COMPARISON ACROSS MODALITIES ($P = 0.04$).

15.3.1.2.1 *Light touch / pressure*

Patients with RH had elevated thresholds to pressure induced pain over the hand dermatomes (median HV = 381 vs. RH = 526; $P = 0.01$) in comparison to healthy controls but not patients with NS (median 408; $P = 0.24$). There was also no difference between patients with NS and healthy controls. Four individual patients with RH and one with NS had elevated sensory thresholds.

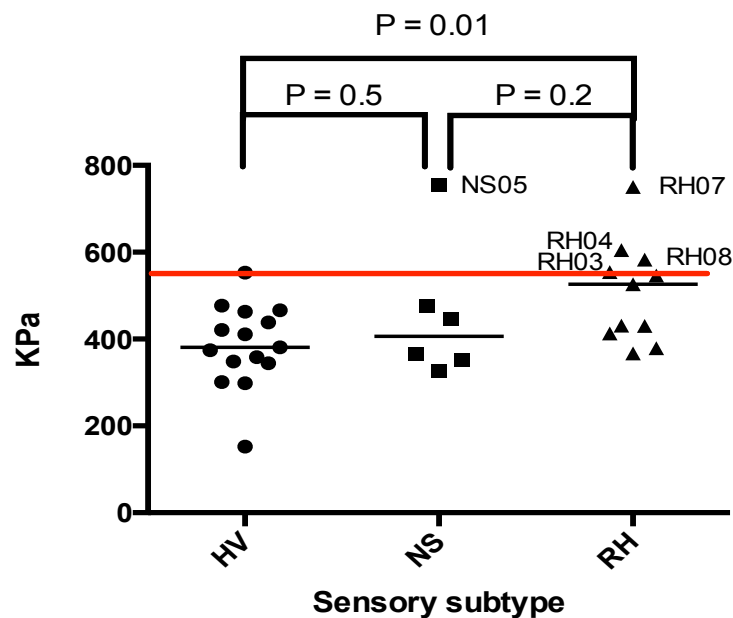


FIGURE 64 – PRESSURE PAIN THRESHOLDS (MEDIAN SHOWN) MEASURED VIA PRESSURE ALGOMETER IN THE C6/C7 DERMATOME IN SUBJECTS STRATIFIED BY SENSORY SUBTYPE

RED LINE = UPPER LIMIT OF NORMAL DETERMINED FROM HV DATA. INDIVIDUAL PATIENT IDENTIFICATION CODES RECORDED FOR THOSE WITH ABNORMAL SENSORY THRESHOLDS TO ALLOW COMPARISON ACROSS MODALITIES ($P=0.04$).

15.3.1.2.2 Electrical stimulation

Patients with RH had elevated sensory thresholds to electrical stimulation of the hand compared to both healthy volunteers (median HV = 2.2 mAmp vs. RH = 3.1 mAmp; $P = 0.03$) and those with NS (median 2.1 mAmp; $P = 0.01$). There was no difference between healthy individuals and patients with normal sensation ($P=0.45$). Three individual patients with RH had abnormal sensory thresholds, as did one patient with NS.

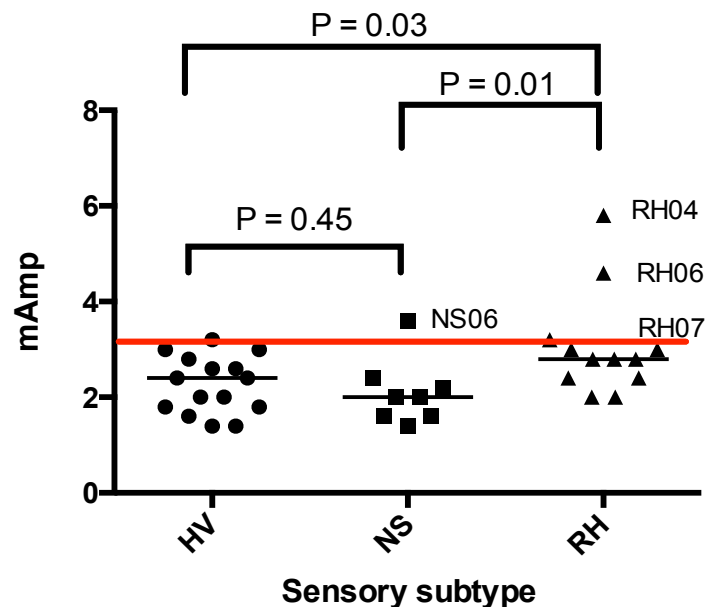


FIGURE 65 – ELECTRICAL SENSORY THRESHOLDS AT THE HAND IN HEALTH VOLUNTEERS AND CONSTIPATED PATIENTS STRATIFIED BY RECTAL SENSORY SUBTYPE

RED LINE = UPPER LIMIT OF NORMAL DETERMINED FROM HV DATA. INDIVIDUAL PATIENT IDENTIFICATION CODES RECORDED FOR THOSE WITH ABNORMAL SENSORY THRESHOLDS TO ALLOW COMPARISON ACROSS MODALITIES ($P=0.02$).

15.3.2 Proposed sensory stratification

When patients were considered as individuals, of the 8 with normal sensation to rectal sensory stimuli, 5 (63%) had entirely normal sacral and peripheral dermatome sensory testing. One subject appeared to have isolated somatic sensory dysfunction with normal visceral sensation, but elevation of both sacral and peripheral dermatome testing. Two other patients with NS had mildly elevated peripheral sensory thresholds in one modality (Von Frey hairs: upper limit of normal = 14 g/mm², patient threshold = 18 g/mm²; electrical sensitivity testing: upper limit of normal 3 mAmp, patient threshold = 3.6 mAmp) without abnormal sacral thresholds.

Of the patients (N = 12) with hyposensitivity, one third (n = 4) had clear elevations of sensory thresholds to both sacral dermatomes and peripheral dermatomes suggesting a systemic sensory neuropathy (RH04, RH06, RH07 and RH12). Six patients had normal somatic nerve testing in both sacral and peripheral dermatomes indicating an isolated visceral abnormality. As seen in those with NS, 2 patients again had mild elevations of thresholds in one modality (upper limit of normal to painful pressure = 553 kPa, patient thresholds: RH03 = 583kPa, RH08 = 554kPa).

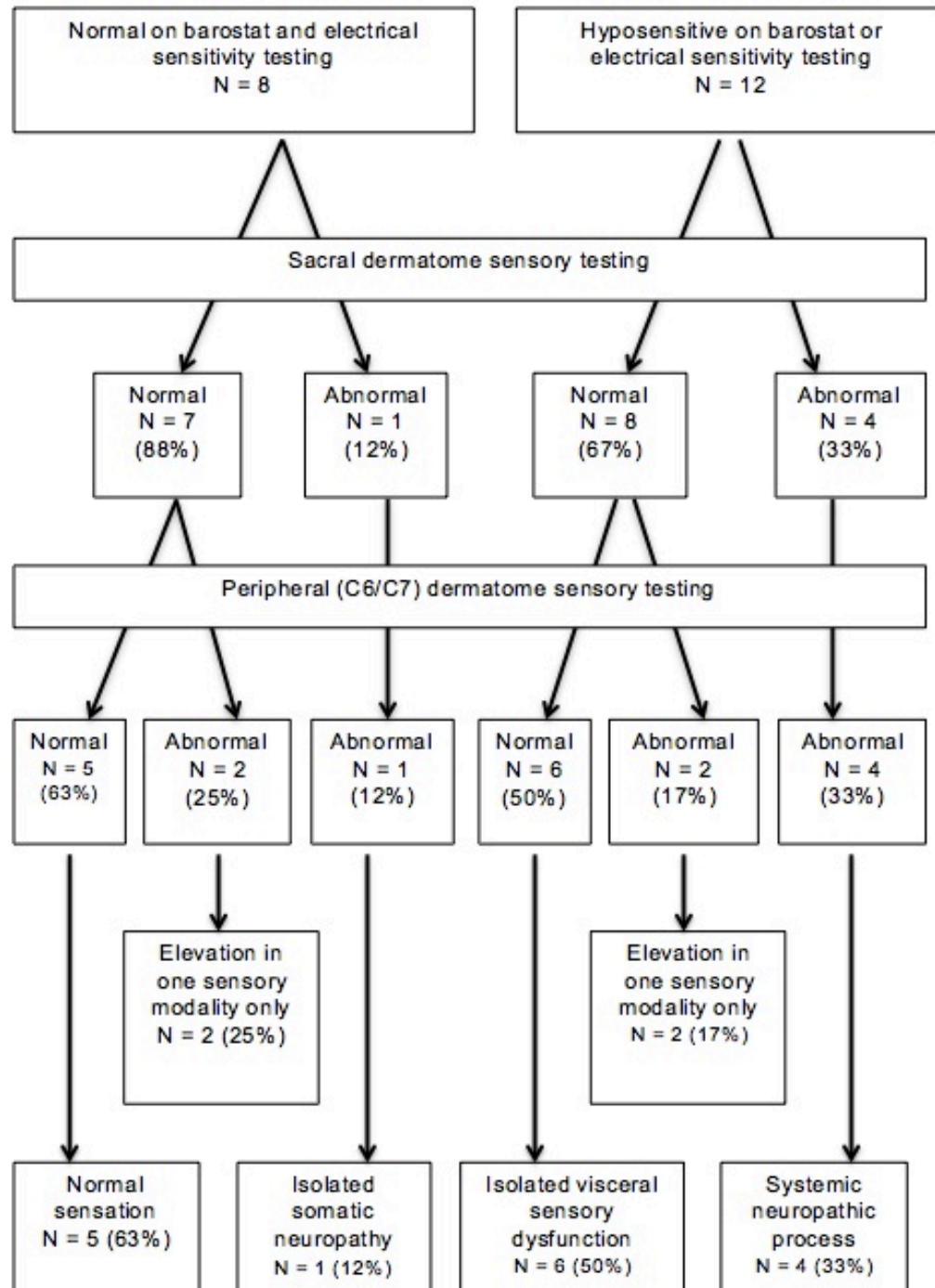


FIGURE 66 – SUMMARY OF RESULTS IN INDIVIDUAL PATIENTS AND PROPOSED SENSORY SUBTYPE.

15.3.3 Assessment of sensory neuronal function

15.3.3.1 Median nerve evoked potentials

Median nerve evoked potentials were successfully recorded in 12 healthy volunteers (two subjects did not elicit an adequate trace, and technical difficulties caused recording failure in a further subject) and all patients. There was no difference in evoked potential morphology, latency (N20: 18.6 vs. 18.4 vs. 18.6, HV, NS and RH respectively; $P=0.86$) or amplitude ($P=0.3$) between groups (Table 24).

TABLE 24 – MEDIAN NERVE EVOKED POTENTIALS PEAK LATENCY AND AMPLITUDE (MEAN \pm SD) IN HEALTHY VOLUNTEERS AND PATIENTS STRATIFIED BY RECTAL SENSORY STATUS.

	HV	NS	RH	P-value
Latency (mean \pm SD)				
P14 (msec)	13.5 \pm 0.6	13.1 \pm 0.4	13.2 \pm 0.7	0.33
N20 (msec)	18.6 \pm 1.2	18.4 \pm 0.7	18.6 \pm 0.6	0.86
Amplitude (mean \pm SD)				
P14 (μV)	0.7 \pm 0.4	0.9 \pm 0.2	0.9 \pm 0.3	0.3
P14 – N20 (μV)	2.1 \pm 0.9	2.5 \pm 0.5	2.4 \pm 0.7	0.43

15.3.3.2 Rectal evoked potential

Four patients with RH did not reach pain threshold at the maximal safety cut off (100 mAmp). In these patients, EP's were performed at 100 mAmp. Overall, successful evoked potential traces were obtained in 12 healthy volunteers, 7 constipated patients with NS and 9 constipated patients with RH ($P = 0.46$). Repeated runs were highly reproducible in each group (Figure 67 Figure 68 Figure 69) with similar morphology between groups. As previously described (Hobday *et al.*, 2002), one patient with hyposensitivity had a biphasic waveform without a discernible P1 peak.

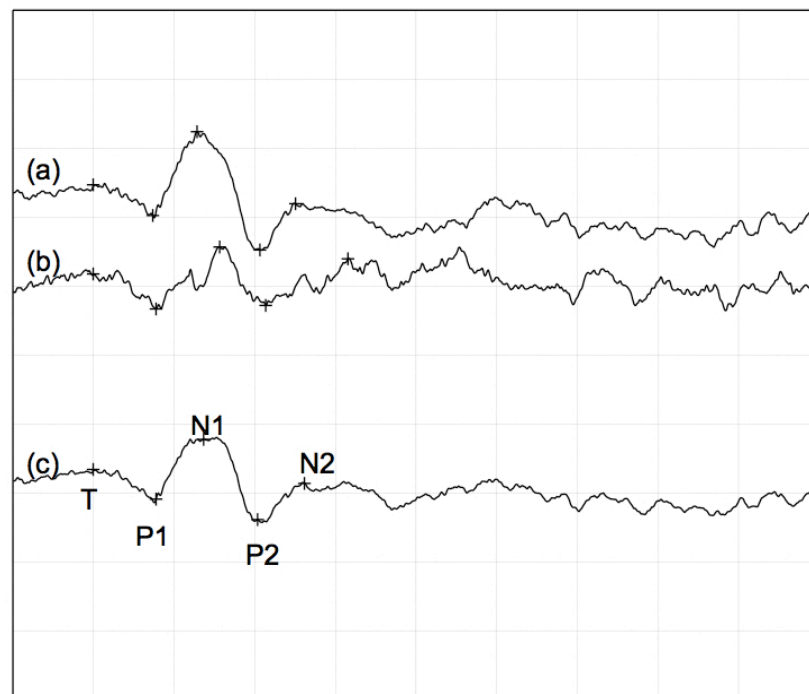


FIGURE 67 – REPRESENTATIVE HEALTHY VOLUNTEER EVOKED POTENTIAL IN RESPONSE TO RECTAL ELECTRICAL STIMULATION.

(A) & (B) = RESULT OF TWO CONSECUTIVE STIMULATION TRIALS. (C) = AVERAGED TRACE. 10 mV/100 msec. T = STIMULATION, P1 = FIRST POSITIVE DEFLECTION, N1 = FIRST NEGATIVE DEFLECTION, P2 = SECOND POSITIVE DEFLECTION, N2 = SECOND NEGATIVE DEFLECTION

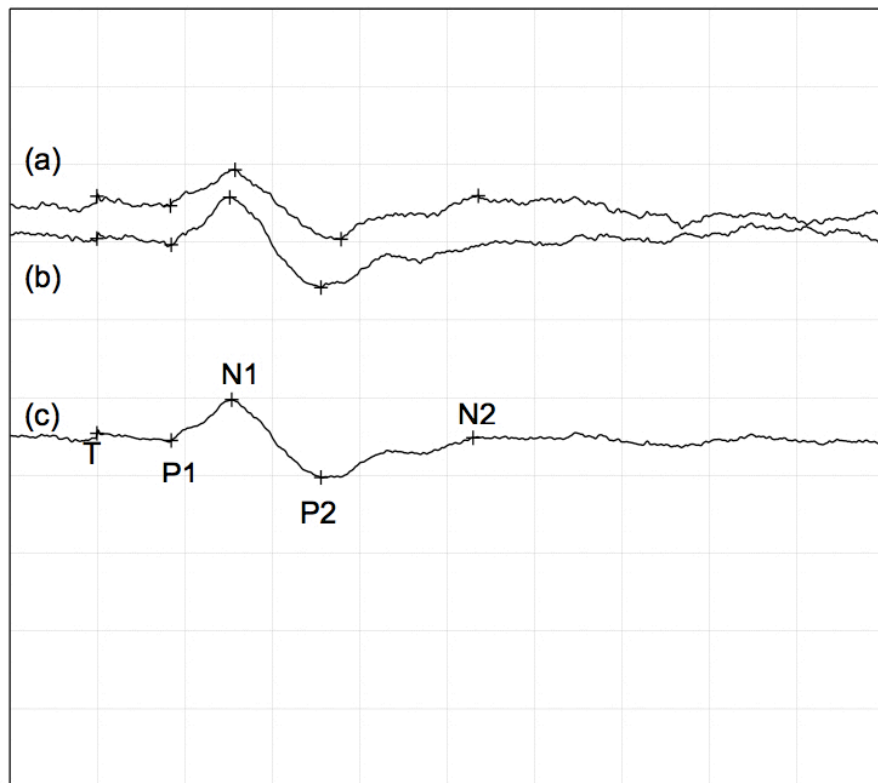


FIGURE 68 – REPRESENTATIVE EVOKED POTENTIAL TRACE IN RESPONSE TO RECTAL ELECTRICAL STIMULATION IN A CONSTIPATED PATIENT WITH NORMAL SENSATION

(A) & (B) = RESULT OF TWO CONSECUTIVE STIMULATION TRIALS. (C) = AVERAGED TRACE. 20 mV/100 msec. T = STIMULATION, P1 = FIRST POSITIVE DEFLECTION, N1 = FIRST NEGATIVE DEFLECTION, P2 = SECOND POSITIVE DEFLECTION, N2 = SECOND NEGATIVE DEFLECTION

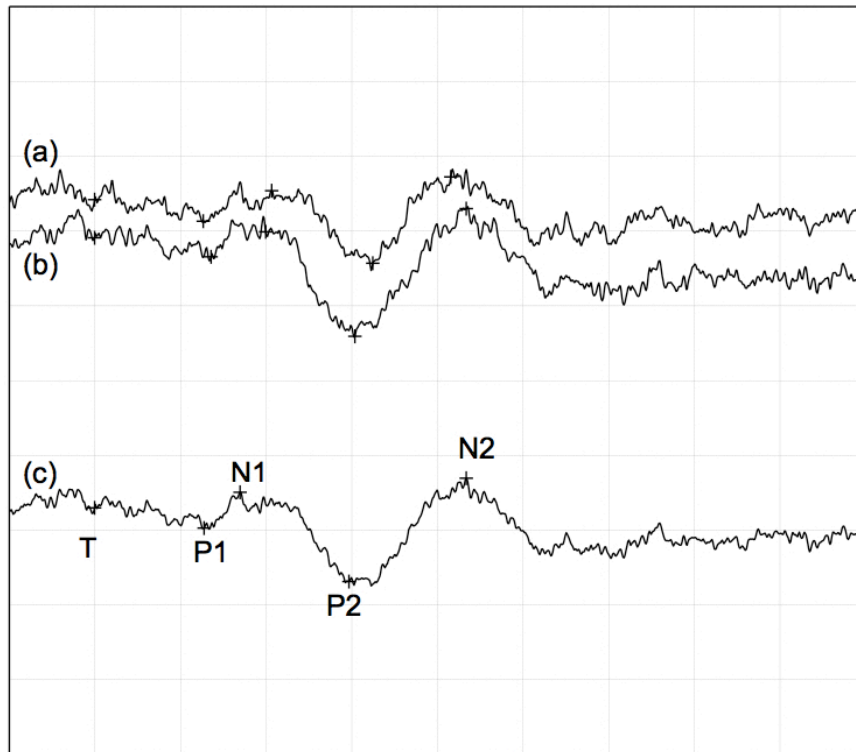


FIGURE 69 – REPRESENTATIVE EVOKED POTENTIAL IN RESPONSE TO RECTAL ELECTRICAL STIMULATION IN A CONSTIPATED PATIENT WITH RECTAL HYPOSENSITIVITY

(A) & (B) = RESULT OF TWO CONSECUTIVE STIMULATION TRIALS. (C) = AVERAGED TRACE. 10 mV/100 msec. T = STIMULATION, P1 = FIRST POSITIVE DEFLECTION, N1 = FIRST NEGATIVE DEFLECTION, P2 = SECOND POSITIVE DEFLECTION, N2 = SECOND NEGATIVE DEFLECTION.

The mean peak latencies for healthy volunteers were: P1 (first downwards deflection) = 83 msec, N1 (first upwards deflection) = 133 msec, P2 (second downwards deflection) = 238 msec and N2 (second upwards deflection) = 339 msec. The mean peak latencies for patients (RH and NS combined) were: P1 = 100 msec, N1 = 156 msec, P2 = 291 msec and N2 = 389 msec; $P=0.11$, $P=0.11$, $p=0.10$ and $P=0.22$, respectively, in comparison to healthy volunteers (Table 24). On *post hoc* analysis, there was a significant delay of the P2 latency in RH patients compared to HV ($P=0.04$). There was no difference in peak-to-peak amplitude between groups.

TABLE 25 – EVOKED POTENTIAL PEAK LATENCIES AND AMPLITUDES (MEAN \pm SD) INDUCED BY RECTAL ELECTRICAL STIMULATION IN HEALTHY VOLUNTEERS AND PATIENTS STRATIFIED BY SENSORY STATUS.

Peak	HV N = 12	NS N = 7	RH N = 9	P – value (all groups)
Latency				
P1 (msec)	83 +/- 31	105 +/- 26	103 +/- 32	0.23
N1 (msec)	133 +/- 40	155 +/- 29	157 +/- 38	0.32
P2 (msec)	238* +/- 54	241 +/- 61	389* +/- 70	0.23
N2 (msec)	339 +/- 97	371 +/- 95	406 +/- 100	0.4

Peak	HV N = 12	NS N = 7	RH N = 9	P – value (all groups)
Amplitude				
P1	2.3 +/- 1.3	2.5 +/- 3.2	1.9 +/- 2.2	0.86
P1 – N1	7.3 +/- 2.6	8.7 +/- 7.1	7.6 +/- 4.6	0.82
N1 – P2	13.2 +/- 7.0	22.7 +/- 17.8	21.1 +/- 13.4	0.26
P2 – N2	8.3 +/- 6.1	13.2 +/- 8.8	14.9 +/- 6.3	0.13

*P2 LATENCY RH vs. HV = P=0.04.

A subgroup analysis comparing healthy volunteers (n = 15) to patients with isolated visceral afferent dysfunction (n = 8) and patients with combined viscerosomatic (generalised) dysfunction (N = 4) was undertaken.

There was no difference in median nerve EP latencies between patients with combined viscerosomatic dysfunction and those with isolated visceral afferent dysfunction (median P14 latency = 13.2 msec in both groups; P = 0.82; median P20 latency = 18.4 msec and 19 msec respectively; P = 0.09)

Patients with isolated visceral afferent dysfunction had prolongation of rectal P1 N1 and P2 latencies compared to healthy volunteers ($P=0.04$, $P=0.17$, $P=0.03$ respectively). Those with combined viscerosomatic neuropathy had rectal P1, N1 and P2 latencies similar to that of healthy volunteers ($P=0.55$, $P=0.94$ and $P=0.07$) (Table 26). There were insufficient data points to perform analysis of the P2 latency due to small subject numbers (not all subjects had a discernible P2).

TABLE 26 – COMPARISON OF RECTAL EP LATENCIES BETWEEN HEALTHY VOLUNTEERS, PATIENTS WITH COMBINED VISEROSOMATIC (GENERALISED) SENSORY DYSFUNCTION AND PATIENTS WITH ISOLATED VISCERAL AFFERENT DYSFUNCTION

Peak	Healthy volunteers (n = 15)	Combined viscerosomatic dysfunction (n = 4)	Isolated visceral afferent dysfunction (n = 8)	P – value (all groups)
Latency (median, range)				
P1	72 (50 – 152)	66 (59 - 106)	106 (80 – 148)	0.07
N1	121 (85 – 198)	119 (107 – 182)	164 (122 - 207)	0.32
P2	254 (150 - 305)	330 (263 – 366)	294 (159 – 321)	0.02

15.3.4 Assessment of anal sphincter integrity and motor function

15.3.4.1 Structural integrity of the anorectal sphincter complex.

All healthy volunteers had an intact anal sphincter complex, as assessed via endoanal ultrasound. One patient with NS had disruption of the external anal sphincter and three had intact but thinned external anal sphincters. One patient with RH had disruption of the internal anal sphincter and one, disruption of the external anal sphincter.

15.3.4.1.1 *Manometry*

There was no difference in maximal anal resting tone (mean HV = 71 cmH₂O, NS = 75 cmH₂O and RH = 79 cmH₂O; P=0.6) or maximal squeeze increment pressures between groups (mean HV = 79 cmH₂O, NS = 77 cmH₂O and RH = 66 cmH₂O; P=0.6).

15.3.4.1.2 *Rectal evacuatory function*

There was no difference in evacuatory time (NS = 101 sec vs. RH = 100 sec; P = 0.9) or percentage of neostool evacuated between sensory groups (NS = 78% vs. RH = 65%; P = 0.1). When considered as individuals, two patients in each group had evacuatory dysfunction (defaecatory time greater than 180 sec or percentage neostool evacuated less than 55%). One patient with NS had a clinically significant rectocoele, two a clinically significant intussusception and one both. In contrast, five

patients with RH had a clinical significant rectocoele, two a significant intussusception and two both.

15.3.4.1.3 Colonic motor function

Within the patient group, 17 had undergone colonic transit testing using radio-opaque markers (7 with normal rectal sensation and 10 with RH). Of those who underwent assessment, all patients with RH (100%) and 57% of those with normal rectal sensation ($P = 0.052$) had delayed colonic transit.

15.3.5 Assessment of motor neuronal function

15.3.5.1 Motor evoked potentials (MEP)

15.3.5.1.1 Lumbosacral

(Figure 70)

Magnetic stimulation was unable to be performed in one HV due to the presence of a large tattoo overlaying the area required for stimulation. A MEP was unable to be recorded in a further 3 healthy volunteers. Furthermore, one patient with constipation and NS and one patient with RH did not produce a satisfactory MEP (of note, cortical MEPs were also unable to be recorded in the same two patients). Overall, while patients had a shorter MEP latency than seen in healthy volunteers, there was no significant difference between groups (Table 27).

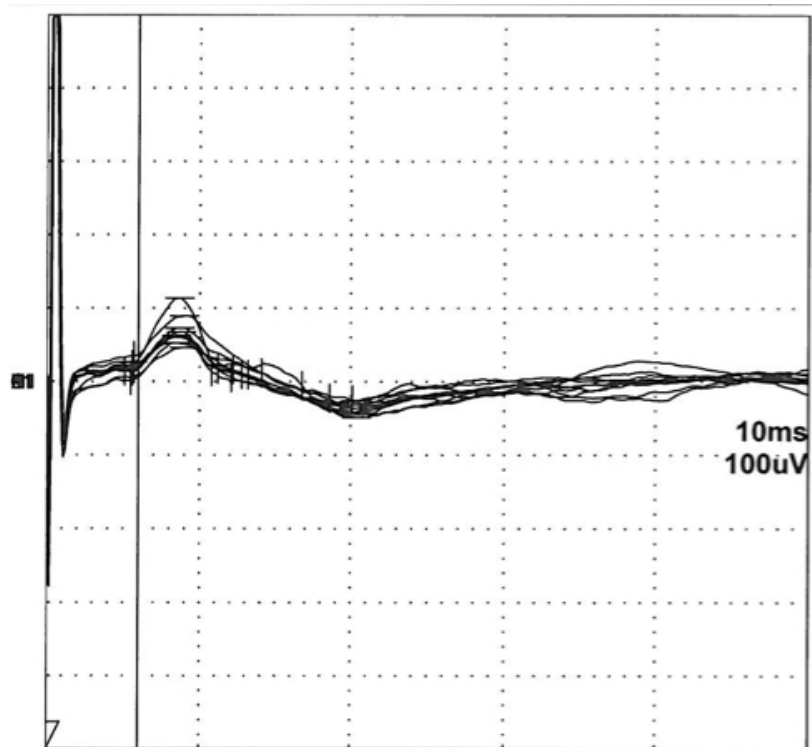


FIGURE 70 – MEP INDUCED FOLLOWING LUMBOSACRAL MAGNETIC STIMULATION IN A HEALTHY VOLUNTEER.

TEN TRIALS DEPICTED. 100uV/10MSEC. LATENCY MEASURED FROM TRIGGER (0 MSEC) TO FIRST DEFLECTION FROM BASELINE.

TABLE 27 – MEP LATENCY IN RESPONSE TO LUMBOSACRAL STIMULATION AND ANAL MOTOR THRESHOLD (BOTH MEAN \pm SD) IN HEALTHY INDIVIDUALS AND PATIENTS STRATIFIED BY RECTAL SENSORY STATUS.

	HV N = 12	NS N = 7	RH N = 11	P - value
Latency (msec)	5.1 +/- 1.8	3.9 +/- 1.1	4.5 +/- 0.8	0.19
Motor threshold	56 +/-15	50 +/- 13	55 +/- 23	0.75

15.3.5.1.2 Cortical

(Figure 71)

Cortical magnetic stimulation was performed in all HV, 7 out of 9 patients with NS (2 patients reported relative contraindications [i.e. family history of epilepsy, jewellery that was unable to be removed]) and 10 out of 12 patients with RH (two patient reported relative contraindications [hearing impairment, metal hair extensions]). An adequate cortical induced MEP was recorded in 10 out of 15 healthy volunteers, 5 out of 7 patients with NS and 7 out of 10 patients with RH (P=0.97)

TABLE 28 – MEP LATENCY IN RESPONSE TO CORTICAL STIMULATION AND ANAL MOTOR THRESHOLD (BOTH MEAN +/- SD) IN HEALTHY INDIVIDUALS AND PATIENTS STRATIFIED BY RECTAL SENSORY STATUS.

	HV N = 10	NS N = 5	RH N = 7	P-value
Latency (msec)	27.9 +/- 4.2	21.2 +/- 2.6	24.4 +/- 4	0.01
Motor threshold	61 +/- 10.4	59 +/- 12	60 +/- 7.1	0.96

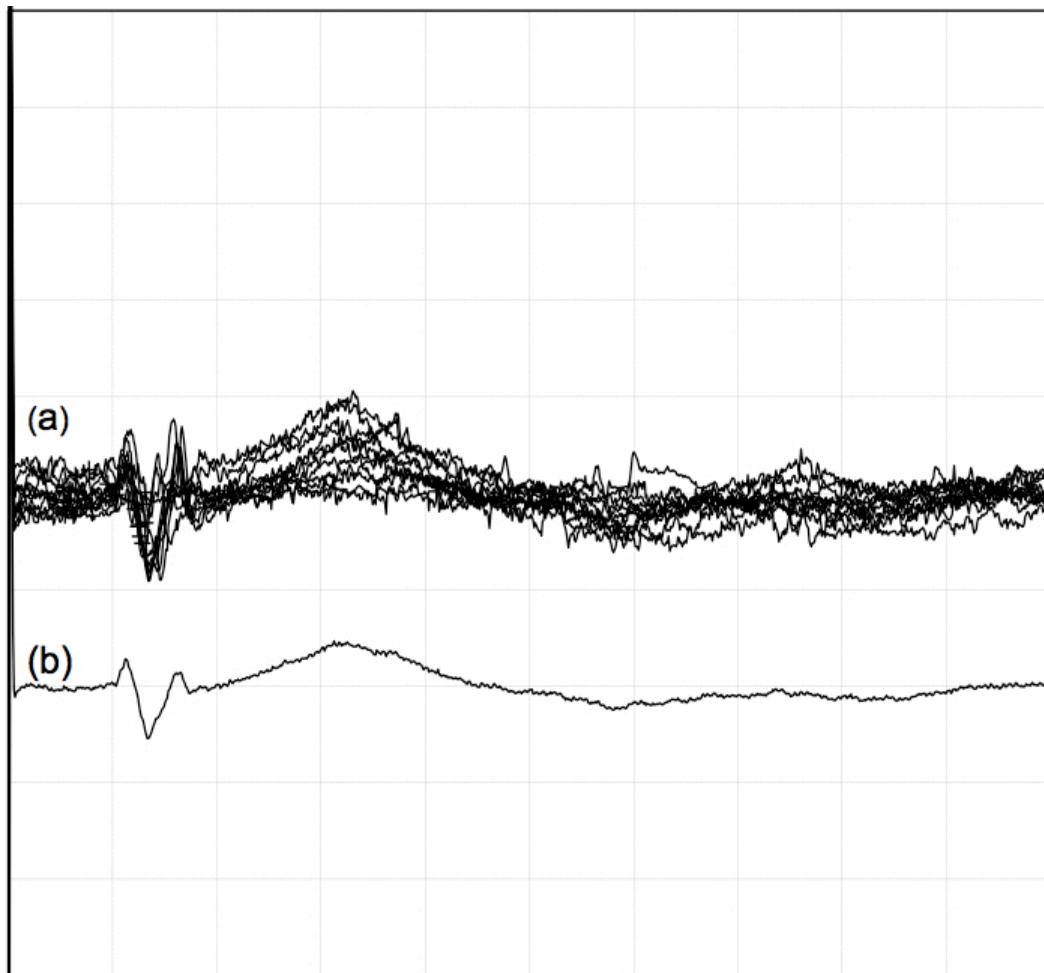


FIGURE 71 – MEP PRODUCED FOLLOWING CORTICAL MAGNETIC STIMULATION OVER CZ IN A HEALTHY VOLUNTEER.

(A) TEN TRACES FOLLOWING MAGNETIC SIMULATION. (B) AVERAGED TRACE. 100 μ V/20MSEC

There was no difference between lumbosacral ($P = 0.21$) or cortical ($P = 0.4$) evoked MEP latencies between patients with combined viscerosensory dysfunction and those with isolated visceral afferent dysfunction.

15.4 Discussion

This pilot is the first study to comprehensively assess somatic sensory function whilst concurrently assessing afferent and efferent visceral neuronal function in highly selected patients with constipation, a proportion of whom had allied impairment of visceral sensory function.

In summary, this study has shown that:

- patients with rectal hyposensitivity (RH) appear to have increased somatic sensory thresholds in the sacral and cervical dermatomes in comparison to healthy volunteers and patients with constipation but normal rectal sensation;
- approximately one third of patients with RH have markedly elevated somatic sensory thresholds, suggestive of a possible generalised sensory neuropathy. The remainder were found to have visceral sensory dysfunction in isolation;
- there was no significant difference in EP latencies between healthy volunteers and patients with constipation either with or without rectal sensory dysfunction
- Patients with combined viscerosomatic afferent dysfunction had rectal evoked potential latencies that were similar to healthy controls, whereas those with isolated visceral afferent dysfunction had a delay in evoked potential latency

- constipated patients had significantly shorter motor evoked latencies to cortical magnetic stimulation than healthy individuals, but there was no impact of rectal sensory status seen
- there was no difference in motor function on measurements of hindgut physiology (colonic transit, evacuation proctography and anal manometry).

Recently, visceral sensitivity (to distension) has been shown to correlate well with somatic sensation (cold and heat sensation of the hand) (Horing *et al.*, 2013) in healthy volunteers; however, this has not been tested previously in patients with hindgut dysfunction and visceral sensory abnormalities. The only prior study to date in constipated patients examined anal sensory function only (Vasudevan *et al.*, 2007), and hence could not determine whether visceral sensory dysfunction was a part of a generalised process. However, the concept of an association between generalised sensory dysfunction and constipation is not new (Raethjen *et al.*, 1997, Knowles *et al.*, 1999), though until now, it has been unclear whether such systemic sensory dysfunction was a feature of constipation *per se*, or whether it reflected visceral sensory impairment.

The present study is able to confirm that, as a group, patients with constipation and RH appear to have higher somatic sensory thresholds in both sacral and peripheral dermatomes indicating a possible generalised somatic neuropathy at least in a proportion (around one third).

Furthermore the results indicate that elevated somatic sensory thresholds do reflect visceral sensory function, rather than constipation itself as patients with normal rectal sensation had generally normal somatic sensory function.

Two-thirds of constipated patients with RH appeared to have visceral afferent dysfunction in isolation indicating that the pathophysiology of RH itself is multifactorial. Indeed, prior literature also supports this hypothesis. For example, a proportion of patients with slow transit constipation (one-third) have previously been shown to have features of small fibre and autonomic neuropathy (Knowles *et al.*, 1999), which has been suggested to be associated with childhood onset of constipation (Raethjen *et al.*, 1997). Unfortunately, most previous studies have not been stratified by rectal sensory status (Altomare *et al.*, 1992, Raethjen *et al.*, 1997, Altomare *et al.*, 1999) with only one study reporting both rectal and somatic sensory function (Knowles *et al.*, 1999). This study showed that somatic sensory abnormalities appeared to be more prevalent in constipated patients with RH in that two-thirds of such patients ($n = 6/9$) were found to have alterations of small fibre function, compared to only one-quarter of patients with normal rectal sensory function ($n = 6/24$).

As shown previously (Chapter 14), evoked potential latencies were longer in constipated patients with RH than healthy controls; however a lack of positive controls (i.e. patients with NS) in this study meant that whether the

delay was associated with visceral sensory dysfunction or constipation *per se* could not be determined. The result of the current study also showed a delay in the P2 peak latency between RH and healthy volunteers. However there was no significant difference between sensory groups. This may be secondary to a type II error due to the limited subjects numbers. A power calculation, based on the current results, indicates that a future study would require at least 34 patients in each group to confidently determine if the null hypothesis (that there is no difference between groups) is correct.

Interestingly, when a sub-analysis was undertaken looking at the association between somatic sensory function and rectal evoked potential traces, patients with isolated visceral afferent dysfunction seemed to have prolongation of rectal evoked potential latencies whereas those with combined viscerosomatic sensory dysfunction generally had EP latencies similar to that of healthy controls. A possible explanation for this could be that combined viscerosomatic dysfunction is mediated via receptor abnormalities; electrical stimulation bypasses the receptor leading to normal evoked potential latencies despite objective measures of afferent dysfunction. In contrast, in those with isolated visceral afferent dysfunction the significantly longer EP latencies may indicate that neuronal dysfunction / injury is more likely.

As stated, it is likely that multiple pathogenic mechanisms underlie the physiological finding of RH. Previous theories regarding pelvic nerve damage, either from straining or surgery (Snooks *et al.*, 1984, Varma and Smith, 1988, Engel and Kamm, 1994, Gee *et al.*, 1995, Amselem *et al.*, 2010), or generalised sensory dysfunction, perhaps related to genetic abnormalities (Camilleri and Fealey, 1990, Raethjen *et al.*, 1997, Knowles *et al.*, 1999, Knowles *et al.*, 2001), may both be correct. The suggestion that blunted rectal sensation is a common symptom of multiple underlying pathologies rather than a disorder in its own right, is not a surprising notion. After all, somatic neuropathy has long been seen as an outcome of numerous conditions (i.e. diabetes, stroke and spinal injury may all cause hypoesthesia).

In contrast to afferent function, there was no difference in visceral motor function between patients stratified by sensory group. Patients with either NS or RH had a similar prevalence of evacuatory dysfunction and anal motor dysfunction and, while there was a trend for an association between RH and slow colonic transit, on direct assessment of the efferent pathway, there was no difference between groups in regards to recorded motor evoked potentials. Overall, this suggests that RH is predominantly a sensory phenomenon. However, this may appear somewhat at odds with the hypothesis that pelvic or spinal nerve damage is responsible for RH. In the pelvis, afferent and efferent nerves run together (Berthoud *et al.*, 2004), and hence if one neuron type is damaged, it is not unreasonable to expect

that the other is also affected. A possible explanation might be that pelvic sensory nerves are more susceptible to damage than motor neurons and thus would be more at risk with compression, stretch or surgical trauma. Certainly this is seen in other peripheral nerve disorders, the most classic being carpal tunnel syndrome (Ginanneschi *et al.*, 2006), where median nerve sensory conduction is often abnormal while motor function remains preserved (Kuntzer, 1994).

Overall, and perhaps unexpectedly, patients (both with and without RH) had shorter latency motor evoked potentials compared to healthy controls (statistically significant for cortical MEPs). This could be explained by increased recruitment of neurons, or alternatively the activation of alternative pathways in patients, but is contrary to prior literature (Coss-Adame *et al.*, 2012), raising the possibility that technical factors may have adversely influenced the outcome. Although patient MEP latencies are similar to those obtained by others (Pelliccioni *et al.*, 1997, Hamdy *et al.*, 1998, Welter *et al.*, 2000, Tantiplachiva *et al.*, 2011, Remes-Troche *et al.*, 2011, Coss-Adame *et al.*, 2012), healthy volunteer data showed marked prolongation of MEP latencies (lumbosacral stimulation: prior studies HV ~3.5 msec vs. present study HV ~5.1 msec; cortical stimulation: prior studies HV ~22.3 msec vs. the present study HV ~ 28 msec (Hamdy *et al.*, 1998, Morren *et al.*, 2001b, Harris *et al.*, 2008, Tantiplachiva *et al.*, 2011, Remes-Troche *et al.*, 2011, Coss-Adame *et al.*, 2012)). This may however, be related to differences in sex and parity between the studies (for

instance, the majority of patients in the Hamdy *et al.* study (Hamdy *et al.*, 1998) were male and any females were nulliparous, whereas the only females were recruited to the present study, of which over half were parous),

Several limitations are apparent. Firstly, the absolute values for EP latencies differed somewhat from results presented previously (Chapter 14). Nevertheless, such differences occurred in parallel in both volunteers and patients. It is possible that the more exacting assessment of sensory status in the present study (barostat and electrical stimulation vs. latex balloon distension alone in Chapter 14) may have contributed to the longer latencies seen in RH patients. However, this would not explain the delay also seen in HV data. It is thus likely that the difference may be explained by variation between recording equipment and the stimulating probe used with each study. Reassuringly, the results of both studies fall within ranges reported previously (Hobday *et al.*, 2002, Harris *et al.*, 2006, Garvin *et al.*, 2010, Remes-Troche *et al.*, 2011, Lelic *et al.*, 2014), although it highlights the importance of developing equipment / unit specific normative data.

This study is also limited by its overall numbers; as a pilot, it was not powered to a specific endpoint. Nevertheless, it provides much useful information to power future studies. It has identified two potential subgroups of patients within the RH population: viscerosomatic (or generalised) neuropathy and isolated visceral dysfunction. This needs to

be confirmed in larger studies, as it is an important distinction; effective therapies for each subgroup may be very different. Neuromodulation, for instance may be more effective in those with isolated visceral sensory dysfunction rather than a generalised disorder (Chang *et al.*, 2003, Lee *et al.*, 2006, Knowles *et al.*, 2012, Jung *et al.*, 2013). It is postulated that receptor dysfunction may be a potential mechanism for sensory dysfunction in patients with generalised sensory neuropathy, given that afferent transmission appeared to be otherwise intact on evoked potential testing. While this is somewhat speculative given the small numbers involved, it warrants targeted investigation in studies with significantly larger subject numbers.

15.5 Conclusions

Approximately one third of patients with RH had features suggestive of a generalised sensory neuropathy and the remainder appeared to have isolated visceral sensory dysfunction. Rectal hyposensitivity, as with somatic neuropathy, may be a common endpoint of multiple pathological processes. Further studies with larger subject numbers are required to accurately identify pathoaetiological mechanisms, be it receptor dysfunction or delayed neuronal transmission, in patients with sensory dysfunction. Precise stratification of rectal afferent function, either secondary to rectal biomechanical changes, primary afferent nerve damage or a generalised sensory neuropathy, is critical to help elucidate

the responsible underlying disease processes. Accurate diagnosis will hopefully allow for the creation of specific targeted therapies to maximise therapeutic success. As such, the clinical assessment of somatic sensory function should be considered fundamental in patients with RH.

16 THESIS OVERVIEW, FUTURE RESEACH OPPORTUNITIES AND OVERALL CONCLUSIONS

16.1 Thesis overview

While the association between rectal hyposensitivity (RH) and hindgut disorders has long been recognised, the impact that impaired visceral sensation has on the clinical presentation of constipation and faecal incontinence has thus far been relatively neglected. Furthermore, although the pathogenesis of RH has previously been hypothesised to involve afferent pathway dysfunction, direct assessment of the transmission of afferent sensory information in patients with RH has never been performed.

The primary aims of this thesis were to determine if RH is:

- clinically important and associated with specific symptoms of constipation and incontinence;
- secondary to afferent neuronal dysfunction; and
- primarily a pelvic afferent abnormality.

Chapter 11

A large case control study, in which consecutive patients, stratified by sensory status, reported frequency of symptoms and overall symptom severity of constipation and incontinence, as well as health status and

quality of life. This was aimed to define the clinical impact of rectal hyposensitivity.

Key findings

In comparison to patients with normal rectal sensation, patients with RH:

- have a higher incidence of constipation;
- describe a higher Cleveland Clinic constipation score, indicating a more severe clinical phenotype;
- more frequently describe specific symptoms of constipation (such as infrequency, hard stools, sense of obstruction to defaecation, ineffective evacuation, incomplete emptying, straining, painful defaecation and abdominal pain);
- report overall poorer health status and quality of life; and
- have a similar incidence and severity of symptoms of faecal incontinence.

Chapter 12

An observational study highlighting the role of rectal hyposensitivity and concurrent constipation in the development of faecal incontinence in males. Symptoms, risk factors and the outcome of physiological investigations were examined.

Key findings

This study demonstrated that in males with faecal incontinence:

- only a minority have anal sphincter dysfunction (45%) as the cause for their symptoms;
- almost 50% report concurrent constipation, suggesting that in many, faecal incontinence may be a secondary phenomenon;
- constipation commonly co-exists in those with RH (77% of patients)
- RH is associated with evacuatory dysfunction (54% of patients), most commonly due to functional obstruction of defaecation; and
- RH is associated with functional anal sphincter weakness (i.e. reduced sphincter tone / function in the absence of structural abnormalities).

Chapter 13

An observational study examining the impact of blunted visceral sensation on the urge to defaecate, as a potential mechanism for symptom generation. Location, quality and intensity of the urge to defaecate were compared between patients with constipation stratified by sensory status, and also healthy volunteers.

Key findings

Analysis of data recorded using the viscerosensory questionnaire revealed that:

- defaecatory urge, in health, generally involves a well defined perianal or rectal sensation most often described as a sense of “fullness”, “pressure” or “heaviness”;

- constipated patients have alteration of the urge to defaecate, noting a more diffuse area in which sensation is experienced and more varied descriptive terms to illustrate quality of sensation compared to healthy volunteers;
- alteration of defaecatory urge is more marked in individuals with rectal sensory dysfunction;
- patients with RH are also more likely to describe absence of the call to stool than patients with normal sensation or healthy volunteers; and
- when examined as individuals, using healthy volunteer data to define normality, 25% of patients with constipation have an abnormal defaecatory urge. This was more common in patients with RH.

Chapter 14

The peripheral transmission of sensory information from the viscera to higher centres was assessed by rectal evoked potentials in patients with rectal hyposensitivity and healthy controls. Subsequent analysis, using inverse modelling techniques, assessed central cortical processing of sensory information.

Key findings

Patients with rectal hyposensitivity have:

- normal median nerve evoked potential latencies;

- delayed rectal evoked potential latencies in comparison to healthy volunteers; and
- no difference in areas of cortical activation on subsequent analysis using inverse modelling techniques.

Chapter 15

A pilot study analysing rectal evoked potentials, results of quantitative somatic sensory testing, motor evoked potentials and assessment of rectal wall biomechanics in healthy volunteers, patients with normal rectal sensation and patients with rectal hyposensitivity, exploring whether RH is secondary to an isolated afferent nerve abnormality or part of a generalised neuropathic disorder.

Key findings

Patients with RH:

- have higher somatic sensory thresholds in the sacral and cervical dermatomes in comparison to healthy volunteers and patients with normal rectal sensation; and
- have no difference in motor function on measurements of hindgut function (colonic transit, evacuation proctography and anal manometry) and direct measures of efferent neuronal transmission.

As a group however, constipated patients have shorter motor evoked latencies than healthy individuals.

Approximately one third of patients with RH appear to have a generalised sensory neuropathy, with the remainder found to have isolated visceral sensory dysfunction

Subgroup analysis of patients with a possible generalised (viscerosomatic) neuropathic disorder, in comparison to those with isolated visceral sensory dysfunction, revealed that patients with a generalised neuropathy have rectal evoked potential latencies similar to that of healthy controls, whereas those with isolated visceral afferent dysfunction have delayed latencies.

16.2 Potential future studies

The epidemiological studies contained within this thesis have established that the presence of sensory dysfunction of the viscera has important clinical implications. In addition, the physiological studies in patients and health have expanded our knowledge of the pathoaetiological mechanisms underscoring blunted visceral sensation.

However, further research is required to determine:

- 1) What is the natural history of RH? Does RH contribute to the development of constipation or is it primarily a marker of severity?*

Currently, the natural history of RH is unknown. While studies have shown that therapies such as biofeedback or sacral nerve stimulation, targeted at sensory function (Chang *et al.*, 2003, Lee *et al.*, 2006, Knowles *et al.*, 2012), result in normalisation of rectal sensory thresholds allied to symptomatic improvement (Rao *et al.*, 1997, Knowles *et al.*, 2012, Ahn *et al.*, 2013), there is little evidence to confirm whether rectal sensory function in the absence of therapeutic intervention is stable or alternatively varies over time. Furthermore, it is not clear whether the presence of RH causes constipation or whether constipation instead leads to the development of RH. For example, do patients with severe constipation, but who initially have normal rectal sensation, become hyposensitive with time? It has been hypothesised that progressive desensitisation of the rectum due to chronic faecal impaction may lead to rectal hyposensitivity. While this is unlikely to be the cause in patients with a generalised sensory neuropathic process underlying RH, this hypothesis may be a possible explanation for RH in patients with isolated blunted visceral sensation and warrants further research.

A longitudinal study recruiting paediatric patients or young adults with constipation would answer many of these questions. Repeat physiological assessment of rectal sensory function over a period of years, correlated with symptom severity scores, would give valuable insights into the role that rectal sensory function plays in symptom generation and the development of chronic constipation.

2) RH appears to be associated with the presence of constipation in patients with incontinence. Do therapies targeted at managing constipation (occult, or otherwise) result in improvement in incontinence symptoms?

Currently, assessment for concurrent constipation is not routinely included during the clinical evaluation of incontinent patients, unless overt symptoms of evacuatory dysfunction are described (Diamant *et al.*, 1999, Tuteja and Rao, 2004). As highlighted in Chapter 12, over 50% of incontinent men with RH have evacuatory dysfunction on proctographic examination, and almost 80% described symptoms of constipation. However, whether empirical therapies targeted to treat constipation in such patients are effective in improving incontinence is unclear. Empirical treatment for rectal evacuatory dysfunction (i.e. biofeedback, laxative therapy) could be hypothesised to result in significant improvement in incontinence symptoms. This could be tested with an interventional study of either / both therapies, with the clinical endpoint being the effect on faecal incontinence severity scores.

3) Further exploration as to the role in which an altered defaecatory urge impacts upon the presentation and / or history of a range of conditions associated with hindgut dysfunction. For instance, is alteration of defaecatory urge found in other hindgut conditions such as irritable bowel syndrome? Is an alteration of defaecatory urge associated with a

longer duration of symptoms or more severe clinical phenotype in constipation? Finally, should normalisation of the call to stool be a therapeutic target and what is the best therapy to achieve this?

The viscerosensory questionnaire is a low-tech patient assessment tool which provides a wealth of information with regards to hindgut function. Patients with constipation clearly have alteration of defaecatory urge, indicating that visceral sensory function is a key component of normal defaecation. However, further work is justified to maximise the clinical impact of such an assessment tool in the care of patients.

More objective definitions of normality, including a combination of location, size of sensory referral area and, most importantly, quality of sensation, should be explored in larger studies. Assessment of patient symptoms, risk factors and family history, correlated with the results acquired from the viscerosensory questionnaire, and also physiological studies may be useful to delineate specific clinical or physiological subgroups.

Further studies are required to determine if the results of the viscerosensory questionnaire predicts response to treatment or alternatively, if effective treatment in patients is associated with normalisation of the description of rectal sensation. Such studies would be critical to determine the importance of such an assessment in ongoing clinical care. Incorporating the questionnaire into a patient's routine

assessment before and after standard current treatment (i.e. laxatives, prokinetics, surgery) or therapies targeted at modification of visceral sensory function (i.e. biofeedback, neuromodulation) may answer many of these questions.

How the results of the viscerosensory questionnaire complements comprehensive physiological assessment of patients, as performed in Chapter 14 and 15, would also be interesting to examine. Approximately 25% of patients with constipation were classified as having an abnormal defaecatory urge. While this was associated with the presence of rectal hyposensitivity to balloon distension, over 50% of patients with RH still had normal defaecatory urge. Although this may be an effect of the criteria by which normality was defined (as discussed above), it may be that abnormal defaecatory urge is instead associated solely with afferent neuronal dysfunction. Patients with RH on latex balloon distension but normal defaecatory urge may thus represent the group in which the “RH” is secondary to rectal biomechanical changes (over 40% of patients with RH on latex balloon distension (Gladman *et al.*, 2009)) such as megarectum. Such patients, would be expected to have otherwise normal afferent function.

4) *Standardised assessment of a large number of patients with RH, using formal quantitative sensory testing protocols are required to accurately*

determine the proportion of patients in which a generalised sensory neuropathic process may occur.

The heterogeneous nature of constipation as a condition has significantly hampered research in the field. As shown in the small pilot study in Chapter 15, it appears that there are at least three pathoetiological subgroups of patients with RH (rectal biomechanical wall abnormalities, generalised afferent neuropathy, and isolated visceral sensory neuropathy) of which there is almost certainly overlap. However results were based on limited subject numbers and did not systematically assess all sensory modalities.

Due to the time consuming nature of formal qualitative sensory testing, it is not yet practical to incorporate such assessment into the routine investigation of patients with constipation. However, a larger scale research study should be commenced to allow more accurate determination of the proportion of patients in which a generalised neuropathic process is contributory. Such a study would also define which sensory modalities are most critical to include within viable clinical testing protocols for the future.

A study should also be considered to compare the results of quantitative sensory testing with that of visceral and somatic evoked potentials. Improved patient numbers, powered to detecting a difference in EP

latencies between groups, would give credence to the hypothesis that a generalised neuropathic process is mediated via afferent receptor dysfunction rather than a neuronal / axonal pathology.

5) Are there specific therapies targeted to treat RH? Can this be predicted based on baseline EP latencies or results of quantitative somatic sensory testing?

Traditionally, constipation therapy has focussed on improving stool consistency and colonic motility (laxatives) or anatomical abnormalities (surgery), whereas abnormal sensory function has been relatively neglected. This is despite studies suggesting that patients with sensory dysfunction are less likely to benefit from such traditional therapies (Akervall *et al.*, 1988). Attempts to normalise rectal sensory function have been shown to result in improvement in symptoms (e.g. with neuromodulation) (Lee *et al.*, 2006, Knowles *et al.*, 2012). Sensory-directed biofeedback therapy has also been objectively shown to benefit constipated patients, with up to 92% of patients showing significant improvement in rectal sensory thresholds (Rao *et al.*, 1997, Peticca and Pescatori, 2002), allied to improvement in symptoms of constipation. The presence of rectal hyposensitivity is also associated with poorer outcomes in patients undergoing surgical procedures such as sphincter repair in incontinent patients (Cohen *et al.*, 1986), or subtotal or total colectomy for the management of constipation (Pluta *et al.*, 1996, Lundin *et al.*, 2002).

However, it is not known whether this is because patients with RH represent a more severe clinical phenotype (as suggested in Chapter 11), resulting in reduced therapeutic response, or rather is as a result of the sensory dysfunction itself. Interestingly, patients with RH seem to respond more favourably to neuromodulation therapy, in that presence of RH predicted success following magnetic sacral nerve stimulation (Lee *et al.*, 2006) or electrical stimulation (Chang *et al.*, 2003). Unfortunately, few constipated patients are currently offered such therapies, thus assessments of such treatments is limited to small patient numbers with only a handful of studies with randomised controlled design. As therapeutic options are limited in this patient group, studies evaluating current treatments with a particular focus on visceral sensation, as well as research aimed at the development of new therapies targeted to afferent dysfunction, should be seen as a priority in this field.

16.3 Conclusions

Rectal hyposensitivity is associated with the presence of constipation and impacts significantly upon clinical presentation. Patients with RH have a more severe symptom phenotype, with worse health status and quality of life in comparison to those with normal visceral sensation. Presence of RH does not influence symptoms of faecal incontinence *per se* suggesting that, in such patients, the presence of incontinence may be a secondary phenomenon related to underlying constipation / faecal impaction. Certainly in males with faecal incontinence, RH and constipation appear to be important contributing mechanisms, with sphincter dysfunction playing a less important role than in females.

The alteration of the urge to defaecate is an important symptom in patients with hindgut dysfunction and is influenced by blunted rectal sensation. Approximately 25% of patients with constipation have an abnormal urge to defaecate and this was significantly more frequently found in those with rectal hyposensitivity than in patients with normal rectal sensation

Patients with RH have delayed afferent nerve transmission, suggesting RH is secondary to a primary afferent disorder. This appears to be an isolated afferent abnormality, as efferent pathway function is unchanged between sensory groups.

A proportion of patients appear to have rectal hyposensitivity as part of a generalised sensory neuropathy whereas the remainder have isolated visceral sensory dysfunction.

Overall this thesis has greatly expanded our understanding of the clinical importance of rectal hyposensitivity. Rectal sensory mechanisms are fundamental to normal hindgut function, and further research aimed to determine if sensory function is an effective therapeutic target in the treatment of chronically constipated patients is warranted.

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18 APPENDIX

Barts and the London Bowel Diary

Name: Appointment date:

Date of Birth: Sex:

This is a diary designed to help us understand more about how you sense the need to open your bowels.

As **soon as you receive this**, please think about filling this in.

We would like you to provide information about **5 visits** to the toilet on different days. Please fill in a single page after the first visit to the toilet on that day. If you go more than once, we only want to know about the first visit. If you go less than once per day, only fill in a page on a day when you visit the toilet. You will find 5 pages to fill in; one for each visit (titled visits 1 – 5).

Please remember to hand this in to the GI Physiology department when you come for your tests.

Thank you

Visit 1

Date:

Time:

am / pm

When you visited the toilet, did you have a feeling / sensation that made you want to go?

☐ Yes – please fill in sections 1 and 2☐ No – please fill in section 2**Section 1**Please carefully **shade** the one or both diagrams below to indicate the location of this sensationHow would you describe this feeling? Please tick any applicable words below or add your own

- | | | | |
|---|---|--|---|
| <input type="checkbox"/> Aching | <input type="checkbox"/> Fullness | <input type="checkbox"/> Prickling | <input type="checkbox"/> Throbbing |
| <input type="checkbox"/> Bloating | <input type="checkbox"/> Heat/burning | <input type="checkbox"/> Sickness/nausea | <input type="checkbox"/> Tickling |
| <input type="checkbox"/> Butterflies/gurgling | <input type="checkbox"/> Heaviness/dragging | <input type="checkbox"/> Spasm | <input type="checkbox"/> Tingling |
| <input type="checkbox"/> Colicky/gripping | <input type="checkbox"/> Irritation | <input type="checkbox"/> Squeezing | <input type="checkbox"/> I can't describe the feeling |
| <input type="checkbox"/> Cramping | <input type="checkbox"/> Pressure | <input type="checkbox"/> Stabbing | |

Other 1 _____

Other 2 _____

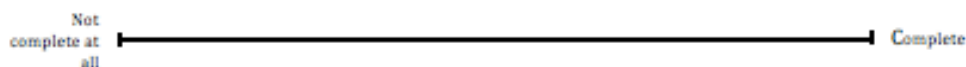
Other 3 _____

How strong was this feeling? Place a vertical mark on the line below to indicate how strong you felt this feeling

**Section 2**Were you successful in opening your bowels?
Did you strain?

no	somewhat	yes
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Was it felt to be complete? Place a vertical mark on the line below to indicate how complete the motion felt



What did the stool look like? Please circle the appropriate image below



hard lumps

formed lumpy

formed cracked

formed soft

soft blobs

mushy

liquid

Visit 2

Date:

Time:

am / pm

When you visited the toilet, did you have a feeling / sensation that made you want to go?

☐ Yes – please fill in sections 1 and 2☐ No – please fill in section 2**Section 1**Please carefully **shade** the one or both diagrams below to indicate the location of this sensationHow would you describe this feeling? Please tick any applicable words below or add your own

- | | | | |
|---|---|--|---|
| <input type="checkbox"/> Aching | <input type="checkbox"/> Fullness | <input type="checkbox"/> Prickling | <input type="checkbox"/> Throbbing |
| <input type="checkbox"/> Bloating | <input type="checkbox"/> Heat/burning | <input type="checkbox"/> Sickness/nausea | <input type="checkbox"/> Tickling |
| <input type="checkbox"/> Butterflies/gurgling | <input type="checkbox"/> Heaviness/dragging | <input type="checkbox"/> Spasm | <input type="checkbox"/> Tingling |
| <input type="checkbox"/> Colicky/gripping | <input type="checkbox"/> Irritation | <input type="checkbox"/> Squeezing | <input type="checkbox"/> I can't describe the feeling |
| <input type="checkbox"/> Cramping | <input type="checkbox"/> Pressure | <input type="checkbox"/> Stabbing | |

Other 1 _____

Other 2 _____

Other 3 _____

How strong was this feeling? Place a vertical mark on the line below to indicate how strong you felt this feeling

No feeling Very strong feeling

Section 2Were you successful in opening your bowels?
Did you strain?

no	somewhat	yes
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Was it felt to be complete? Place a vertical mark on the line below to indicate how complete the motion felt

Not complete at all Complete

What did the stool look like? Please circle the appropriate image below



hard lumps

formed lumpy

formed cracked

formed soft

soft blobs

mushy

liquid

Visit 3

Date:

Time:

am / pm

When you visited the toilet, did you have a feeling / sensation that made you want to go?

☐ Yes – please fill in sections 1 and 2☐ No – please fill in section 2**Section 1**Please carefully **shade** the one or both diagrams below to indicate the location of this sensationHow would you describe this feeling? Please tick any applicable words below or add your own

- | | | | |
|---|---|--|---|
| <input type="checkbox"/> Aching | <input type="checkbox"/> Fullness | <input type="checkbox"/> Prickling | <input type="checkbox"/> Throbbing |
| <input type="checkbox"/> Bloating | <input type="checkbox"/> Heat/burning | <input type="checkbox"/> Sickness/nausea | <input type="checkbox"/> Tickling |
| <input type="checkbox"/> Butterflies/gurgling | <input type="checkbox"/> Heaviness/dragging | <input type="checkbox"/> Spasm | <input type="checkbox"/> Tingling |
| <input type="checkbox"/> Colicky/gripping | <input type="checkbox"/> Irritation | <input type="checkbox"/> Squeezing | <input type="checkbox"/> I can't describe the feeling |
| <input type="checkbox"/> Cramping | <input type="checkbox"/> Pressure | <input type="checkbox"/> Stabbing | |

Other 1 _____

Other 2 _____

Other 3 _____

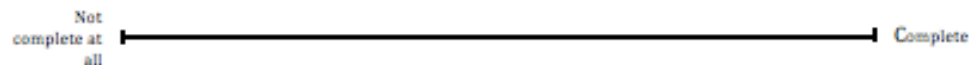
How strong was this feeling? Place a vertical mark on the line below to indicate how strong you felt this feeling

**Section 2**Were you successful in opening your bowels?
Did you strain?

no somewhat yes

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
--------------------------	--------------------------	--------------------------

Was it felt to be complete? Place a vertical mark on the line below to indicate how complete the motion felt



What did the stool look like? Please circle the appropriate image below



hard lumps

formed lumpy

formed cracked

formed soft

soft blobs

mushy

liquid

Visit 4

Date:

Time:

am / pm

When you visited the toilet, did you have a feeling / sensation that made you want to go?

☐ Yes - please fill in sections 1 and 2☐ No - please fill in section 2**Section 1**Please carefully **shade** the one or both diagrams below to indicate the location of this sensationHow would you describe this feeling? Please tick any applicable words below or add your own

- | | | | |
|---|---|--|---|
| <input type="checkbox"/> Aching | <input type="checkbox"/> Fullness | <input type="checkbox"/> Prickling | <input type="checkbox"/> Throbbing |
| <input type="checkbox"/> Bloating | <input type="checkbox"/> Heat/burning | <input type="checkbox"/> Sickness/nausea | <input type="checkbox"/> Tickling |
| <input type="checkbox"/> Butterflies/gurgling | <input type="checkbox"/> Heaviness/dragging | <input type="checkbox"/> Spasm | <input type="checkbox"/> Tingling |
| <input type="checkbox"/> Colicky/gripping | <input type="checkbox"/> Irritation | <input type="checkbox"/> Squeezing | <input type="checkbox"/> I can't describe the feeling |
| <input type="checkbox"/> Cramping | <input type="checkbox"/> Pressure | <input type="checkbox"/> Stabbing | |

Other 1 _____

Other 2 _____

Other 3 _____

How strong was this feeling? Place a vertical mark on the line below to indicate how strong you felt this feeling

No feeling Very strong feeling

Section 2Were you successful in opening your bowels?
Did you strain?

no	somewhat	yes
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Was it felt to be complete? Place a vertical mark on the line below to indicate how complete the motion felt

Not complete at all Complete

What did the stool look like? Please circle the appropriate image below



hard lumps formed lump formed cracked formed soft soft blobs mushy liquid

Visit 5

Date:

Time:

am / pm

When you visited the toilet, did you have a feeling / sensation that made you want to go?

☐ Yes - please fill in sections 1 and 2☐ No - please fill in section 2**Section 1**Please carefully **shade** the one or both diagrams below to indicate the location of this sensationHow would you describe this feeling? Please tick any applicable words below or add your own

- | | | | |
|---|---|--|---|
| <input type="checkbox"/> Aching | <input type="checkbox"/> Fullness | <input type="checkbox"/> Prickling | <input type="checkbox"/> Throbbing |
| <input type="checkbox"/> Bloating | <input type="checkbox"/> Heat/burning | <input type="checkbox"/> Sickness/nausea | <input type="checkbox"/> Tickling |
| <input type="checkbox"/> Butterflies/gurgling | <input type="checkbox"/> Heaviness/dragging | <input type="checkbox"/> Spasm | <input type="checkbox"/> Tingling |
| <input type="checkbox"/> Colicky/gripping | <input type="checkbox"/> Irritation | <input type="checkbox"/> Squeezing | <input type="checkbox"/> I can't describe the feeling |
| <input type="checkbox"/> Cramping | <input type="checkbox"/> Pressure | <input type="checkbox"/> Stabbing | |

Other 1 _____

Other 2 _____

Other 3 _____

How strong was this feeling? Place a vertical mark on the line below to indicate how strong you felt this feeling

No feeling Very strong feeling

Section 2Were you successful in opening your bowels?
Did you strain?

no	somewhat	yes
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Was it felt to be complete? Place a vertical mark on the line below to indicate how complete the motion felt

Not complete at all Complete

What did the stool look like? Please circle the appropriate image below



hard lumps

formed lumpy

formed cracked

formed soft

soft blobs

mushy

liquid